COMPOSITIONS AND METHODS FOR INHIBITING G2 CELL CYCLE ARREST AND SENSITIZING CELLS TO DNA DAMAGING AGENTS

TECHNICAL FIELD

This invention generally pertains to the fields of medicine and cancer therapeutics. In particular, this invention provides novel genes and polypeptides and methods for making and using them. Specifically, the compositions and methods of the invention are used to treat disorders of cell growth, such as cancer. In particular, the invention provides methods for selectively sensitizing G1 checkpoint impaired cancer cells to DNA damaging agents and treatments. Also provided are methods for screening for compounds able to interact with, e.g., inhibit, enzymes involved in the G2 cell cycle arrest checkpoint, such as Chk1 and/or Chk2/Cds1 kinase.

BACKGROUND

It is a continuing challenge to develop anti-cancer agents that are capable of inhibiting the growth of, or killing, cancer cells, without affecting normal cells. Researchers have focused on genetic mutations in cancer cells to find clues to discover such new anti-cancer drugs.

Many cancer cells have mutations in genes involved in the G1 cell cycle arrest checkpoint. Such genes include impaired tumor suppressor genes, e.g., p53, Rb, $p16^{INK4}$, and $p19^{ARF}$. Alternatively, such mutations can cause expression of oncogenes, e.g., MDM-2 and cyclin D. In addition to these, excessive growth factor signaling can be caused by the over expression of growth factors. Together with these gain-of-function mutations, growth factor receptors or downstream signal-transducing molecules can cause cell transformation by overriding the G1 checkpoint. In contrast, few cancers have disrupted G2 cell cycle arrest checkpoints. Thus, the G2 checkpoint is usually retained in cancer cells with the impaired G1 checkpoint.

compared to normal cells (with intact G1), since progression through G1 and G2 without

repairing such damage induces apoptosis.

The mechanism that promotes the cell cycle G2 arrest after DNA damage is conserved among species from yeast to human. In the presence of damaged DNA, Cdc2/Cyclin B kinase is kept inactive because of inhibitory phosphorylation of threonine-14 and tyrosine-15 residues on Cdc2 kinase. At the onset of mitosis, the dual phosphatase Cdc25 kinase removes these inhibitory phosphates and thereby activates Cdc2/Cyclin B kinase.

In fission yeast, the protein kinase Chk1 is required for the cell cycle arrest in response to damaged DNA. Chk1 kinase acts downstream of several rad gene products and is modified by the phosphorylation upon DNA damage. The kinases Rad53 of budding yeast and Cds1 of fission yeast are known to conduct signals from unreplicated DNA. It appears that there is some redundancy between Chk1 and Cds1 because elimination of both Chk1 and Cds1 was culminated in disruption of the G2 arrest induced by damaged DNA. Interestingly, both Chk1 and Cds1 phosphorylate Cdc25 kinase and promote Rad24 binding to Cdc25, which sequesters Cdc25 to cytosol and prevents Cdc2/Cyclin B activation. Therefore Cdc25 appears to be a common target of theses kinases and presumably an indispensable factor in the G2 checkpoint.

In humans, both hChk1, a human homologue of fission yeast Chk1, and Chk2/HuCds1, a human homologue of the budding yeast Rad53 and fission yeast Cds1, phosphorylate Cdc25C at serine-216, a critical regulatory site, in response to DNA damage. This phosphorylation creates a binding site for small acidic proteins 14-3-3s, human homologues of Rad24 and Rad25 of fission yeast (Lopez-Girona (1999) Nature 397:172-175). The regulatory role of this phosphorylation was clearly indicated by the fact that substitution of serine-216 to alanine on Cdc25C disrupted cell cycle G2 arrest in human cells (Peng (1997) Science 277:1501-1505).

SUMMARY

This invention provides nucleic acids and polypeptides which can be used to

the invention can function by inhibiting the G2 cell cycle arrest checkpoint. Thus, the

invention also provides compositions and methods for selectively sensitizing a cell with an impaired G1 cell cycle arrest checkpoint, e.g., a cancer cell, to a DNA damaging agent

The invention provides an isolated or recombinant polypeptide comprising the amino acid sequence: X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11}, wherein X1 is L, F, W, M, R, I, V, Y, K, or absent, X2 is Y, F, A, W, S or T, X3 is any amino acid, X4 is any amino acid, X5 is any amino acid, X6 is S, A, N, H or P, X7 is any amino acid, X8 is any amino acid, X9 is any amino acid or absent, X10 is N, G, L, S, M, P, N, A or absent, and X11 is L or absent, wherein the polypeptide when administered to or expressed in a cell disrupts the G2 cell cycle arrest checkpoint.

In alternative embodiments, for the isolated or recombinant polypeptide of the invention: X_1 is L, F, W, M, R or absent or X_1 is L, F or W; X_2 is Y, F, A; X_3 is R, T, S, H, D, G, A, L, K, A, N, Q or P, or, X_3 is R, T, S, H, D, G, A or L, or, X_3 is R, T, S or H; X_4 is S, T, G, A, L, R, I, M, V, P, or, X_4 is S, T, G, A, L, R, or, X_4 is S; X_5 is P, A, G, S or T, or, X_5 is P; X_6 is S, N, H, P, A, G or T, or, X_6 is S, N or H, or, X_6 is S; X_7 is M, F, Y, D, E, N, Q, H, G, I, L, V, A, P, N or W, or, X_7 is M, F, Y, D, E, N, Q or H, or, X_7 is M, F, Y, Q or H; X_8 is P, F, Y, W, L, G, M, D, E, N, Q, H, I, V, A or P, or, X_8 is P, F, Y or W, or, X_8 is Y; X_9 is E, G, L, S, M, P, N, D, A, T, P or absent; X_{10} is absent; X_{11} is absent.

In one embodiment, the invention provides a polypeptide wherein X_2 is Y, X_5 is P, and X_{10} is N. In one embodiment, the invention provides a polypeptide wherein X_3 is R, X_8 is P, and X_{11} is L. In one embodiment, the invention provides a polypeptide wherein X_4 is S, X_5 is P, X_6 is S, X_9 is E, X_{10} is N and X_{11} is L.

In alternative embodiments, the invention provides an isolated or recombinant polypeptide wherein the amino acid sequence comprises Y G G P G G G G N (SEQ ID NO: 1895); R Y S L P P E L S N M (SEQ ID NO: 1); L A R S A S M P E A L (SEQ ID NO: 1896); L Y R S P S M P E N L (SEQ ID NO: 2); L Y R S P A M P E N L (SEQ ID NO: 1897); W Y R S P S F Y E N L (SEQ ID NO: 904); W Y R S P S Y Y E N L (SEQ ID NO: 908); or, W Y R S P S Y Y (SEQ ID NO: 1898).

In alternative embodiments, the invention provides an isolated or recombinant

R S P S Y W E N L (SEQ ID NO: 35).

In alternative embodiments, the invention provides an isolated or recombinant polypeptide wherein the amino acid sequence comprises L Y R S P S N P E N L (SEQ ID NO: 22), L Y R S P S N F E N L (SEQ ID NO: 23), L Y R S P S N Y E N L (SEQ ID NO: 24), or L Y R S P S N W E N L (SEQ ID NO: 25).

In alternative embodiments, the invention provides an isolated or recombinant polypeptide wherein the amino acid sequence comprises L Y R S P S H P E N L (SEQ ID NO: 30), L Y R S P S H F E N L (SEQ ID NO: 31), L Y R S P S H Y E N L (SEQ ID NO: 32), L Y R S P S H W E N L (SEQ ID NO: 33), L Y S S P S M P E N L (SEQ ID NO: 34), L Y S S P S M F E N L (SEQ ID NO: 35), L Y S S P S M Y E N L (SEQ ID NO: 36), L Y S S P S M W E N L (SEQ ID NO: 37), L Y S S P S F P E N L (SEQ ID NO: 38), L Y S S P S F P E N L (SEQ ID NO: 38), L Y S S P S F F E N L (SEQ ID NO: 39), L Y S S P S F Y E N L (SEQ ID NO: 40), L Y S S P S F W E N L (SEQ ID NO: 41), L Y S S P S Y P E N L (SEQ ID NO: 42), L Y S S P S Y F E N L (SEQ ID NO: 43), L Y S S P S Y Y E N L (SEQ ID NO: 44), or L Y S S P S Y W E N L (SEQ ID NO: 45) .

In alternative embodiments, the invention provides an isolated or recombinant polypeptide wherein the amino acid sequence comprises L Y S S P S Q P E N L (SEQ ID NO: 58), L Y S S P S Q W E N L (SEQ ID NO: 61), L Y S S P S H P E N L (SEQ ID NO: 62), L Y S S P S H F E N L (SEQ ID NO: 63), L Y S S P S H Y E N L (SEQ ID NO: 64), L Y S S P S H W E N L (SEQ ID NO: 65), L Y T S P S M P E N L (SEQ ID NO: 66), L Y T S P S M F E N L (SEQ ID NO: 67), L Y T S P S M Y E N L (SEQ ID NO: 68), L Y T S P S M W E N L (SEQ ID NO: 69), L Y T S P S F P E N L (SEQ ID NO: 70), L Y T S P S F F E N L (SEQ ID NO: 71), L Y T S P S F Y E N L (SEQ ID NO: 72), L Y T S P S F W E N L (SEQ ID NO: 73), L Y T S P S Y P E N L (SEQ ID NO: 74), L Y T S P S Y F E N L (SEQ ID NO: 75), L Y T S P S Y Y E N L (SEQ ID NO: 76), or L Y T S P S Y W E N L (SEQ ID NO: 77) .

In alternative embodiments, the invention provides an isolated or recombinant polypeptide wherein the amino acid sequence comprises L Y T S P S N P E N L (SEQ ID NO: 86), L Y T S P S N F E N L (SEQ ID NO: 87), L Y T S P S N Y E N L (SEQ ID NO: 88) or L Y T S P S N W E N L (SEQ ID NO: 89).

94), L Y T S P S H F E N L (SEQ ID NO: 95), L Y T S P S H Y E N L (SEQ ID NO: 96) or L Y T S P S H W E N L (SEQ ID NO: 97).

In alternative embodiments, the invention provides an isolated or recombinant polypeptide wherein the amino acid sequence comprises L Y H S P S Y P E N L (SEQ ID NO: 106), L Y H S P S Y F E N L (SEQ ID NO: 107), L Y H S P S Y Y E N L (SEQ ID NO: 108) or L Y H S P S Y W E N L (SEQ ID NO: 109).

In alternative embodiments, the invention provides an isolated or recombinant polypeptide wherein the amino acid sequence comprises L F T S P S Y P E N L (SEQ ID NO: 298), L F T S P S Y F E N L (SEQ ID NO: 299), L F T S P S Y Y E N L (SEQ ID NO: 300) or L F T S P S Y W E N L (SEQ ID NO: 301).

In alternative embodiments, the invention provides an isolated or recombinant polypeptide wherein the amino acid sequence comprises F Y S S P S H P E N L (SEQ ID NO: 510), F Y S S P S H F E N L (SEQ ID NO 511), F Y S S P S H Y E N L (SEQ ID NO: 512), F Y S S P S H W E N L (SEQ ID NO: 513), F Y T S P S M P E N L (SEQ ID NO: 514), F Y T S P S M F E N L (SEQ ID NO: 515), F Y T S P S M Y E N L (SEQ ID NO: 516), F Y T S P S M W E N L (SEQ ID NO: 517), F Y T S P S F P E N L (SEQ ID NO: 518), F Y T S P S F F E N L (SEQ ID NO: 519), F Y T S P S F Y E N L (SEQ ID NO: 520), F Y T S P S F W E N L (SEQ ID NO: 521), F Y T S P S Y P E N L (SEQ ID NO 522), F Y T S P S Y F E N L (SEQ ID NO: 523), F Y T S P S Y Y E N L (SEQ ID NO: 524) or F Y T S P S Y W E N L (SEQ ID NO: 525).

In alternative embodiments, the invention provides an isolated or recombinant polypeptide wherein the amino acid sequence comprises W Y R S P S M P E N L (SEQ ID NO: 898), W Y R S P S M F E N L (SEQ ID NO: 899), W Y R S P S M Y E N L (SEQ ID NO: 900), W Y R S P S M W E N L (SEQ ID NO: 901), W Y R S P S F P E N L (SEQ ID NO: 902), W Y R S P S F F E N L (SEQ ID NO: 903), W Y R S P S F Y E N L (SEQ ID NO: 904), W Y R S P S F W E N L (SEQ ID NO: 905), W Y R S P S Y P E N L (SEQ ID NO: 906), W Y R S P S Y F E N L (SEQ ID NO: 907), W Y R S P S Y Y E N L (SEQ ID NO: 908) or W Y R S P S Y W E N L (SEQ ID NO: 909).

In alternative embodiments, the invention provides an isolated or recombinant

904), W Y I S P S M W E N L (SEQ ID NO: 905), W Y I S P S F P E N L (SEQ ID NO: 906),

W Y T S P S F F E N L (SEQ ID NO: 967), W Y T S P S F Y E N L (SEQ ID NO: 968), W Y T S P S F W E N L (SEQ ID NO: 969), W Y T S P S Y P E N L (SEQ ID NO: 970), W Y T S P S Y F E N L (SEQ ID NO: 971), W Y T S P S Y Y E N L (SEQ ID NO: 972) or W Y T S P S Y W E N L (SEQ ID NO: 973).

In alternative embodiments, the invention provides an isolated or recombinant polypeptide wherein the amino acid sequence comprises W Y T S P S H P E N L (SEQ ID NO: 990), W Y T S P S H F E N L (SEQ ID NO: 991), W Y T S P S H Y E N L (SEQ ID NO: 992) or W Y T S P S H W E N L (SEQ ID NO: 993).

In alternative embodiments, the invention provides an isolated or recombinant polypeptide wherein the amino acid sequence comprises L K R S P S M P E N L (SEQ ID NO: 1826), L Y I S P S M P E N L (SEQ ID NO: 1844) or L Y R S P S M V E N L (SEQ ID NO: 1894).

In one embodiment, the invention provides an isolated or recombinant polypeptide wherein the polypeptide when administered to or expressed in a cell disrupts the G2 cell cycle arrest checkpoint, wherein the cell is a mammalian cell. The cell can be a human cell, a yeast cell, an insect cell, a bacterial cell, a plant cell, and the like.

In one embodiment, the invention provides an isolated or recombinant polypeptide further comprising a cell membrane permeant. The cell membrane permeant can comprise a polypeptide, such as a TAT protein transduction domain, e.g., comprising a sequence Y G R K K R R Q R R R (SEQ ID NO: 1899). Alternatively, the cell membrane permeant can comprise a lipid, such as a liposome.

The invention provides a chimeric polypeptide comprising a first domain comprising a polypeptide of the invention and a second domain comprising a cell membrane permeant, wherein the polypeptide when administered to or expressed in a cell disrupts the G2 cell cycle arrest checkpoint. The chimeric polypeptide can be a recombinant fusion protein.

The invention provides an isolated or recombinant nucleic acid encoding a polypeptide or a chimeric polypeptide of the invention, wherein the polypeptide, when administered to or expressed in a cell, disrupts the G2 cell cycle arrest checkpoint

when administered to or expressed in a cell, disrupts the G2 cell cycle arrest checkpoint.

The invention provides a cell comprising a nucleic acid or an expression vector of the invention. The cell can be a bacterial, a yeast, an insect, a plant, or a mammalian cell.

The invention provides a pharmaceutical composition comprising a polypeptide of the invention, a nucleic acid of the invention, an expression vector of the invention, or a cell of the invention; and, a pharmaceutically acceptable excipient. In one embodiment, the pharmaceutical composition can comprise a liposome.

The invention provides a method for inhibiting a the activity of a Chk1 kinase or a Chk2 kinase comprising contacting the kinase with a polypeptide of the invention or a pharmaceutical composition of the invention, in an amount sufficient to inhibit the activity of the Chk1 or Chk2 kinase.

The invention provides a method for disrupting a cell G2 cell cycle arrest checkpoint comprising contacting the cell with a polypeptide of the invention or a pharmaceutical composition of the invention in an amount sufficient to disrupt the G2 cell cycle arrest checkpoint. In alternative embodiments the cell is a mammalian cell, a human cell or a cancer cell.

The invention provides a method for sensitizing a cell to a DNA damaging agent comprising contacting the cell with a polypeptide of the invention or a pharmaceutical composition of the invention in an amount sufficient to disrupt the G2 cell cycle arrest checkpoint, thereby sensitizing the cell to the DNA damaging agent. In alternative embodiments the cell is a mammalian cell, a human cell or a cancer cell. The cancer cell can have an impaired G1 cell cycle arrest checkpoint.

The invention provides a method for selectively sensitizing a cell with an impaired G1 cell cycle arrest checkpoint to a DNA damaging agent comprising contacting the cell with a polypeptide of the invention or a pharmaceutical composition of the invention, in an amount sufficient to disrupt the G2 cell cycle arrest checkpoint, thereby sensitizing the cell to the DNA damaging agent. In alternative embodiments the cell is a mammalian cell, a human cell or a cancer cell.

composition of the invention, in an amount sufficient to disrupt the G2 cell cycle arrest

checkpoint in the cancer cell, thereby sensitizing the cancer cell to a DNA damaging agent, and administering a DNA damaging agent. In alternative embodiments the cell is a mammalian cell, a human cell or a cancer cell. The cancer cell can have an impaired G1 cell cycle arrest checkpoint. The DNA damaging agent can be 5-fluorouracil (5-FU), rebeccamycin, adriamycin, bleomycin, cisplatin, hyperthermia, UV irradiation or gamma-irradiation.

The invention provides a method for screening for compounds capable of modulating the activity of a Chk1 kinase or a Chk2 kinase comprising the following steps: (a) providing a test compound; (b) providing a Chk1 kinase or a Chk2 kinase; (c) providing a polypeptide of the invention, wherein the polypeptide binds to the Chk1 kinase or the Chk2 kinase; and, (d) contacting the test compound with the kinase and the polypeptide and measuring the ability of the test compound to prevent binding of the polypeptide to the kinase.

The invention provides a method for screening for compounds capable of modulating the activity of a Chk1 kinase or a Chk2 kinase comprising the following steps: (a) providing a test compound; (b) providing a Chk1 kinase or a Chk2 kinase; (c) providing a polypeptide of the invention, wherein the polypeptide is phosphorylated by the Chk1 kinase or the Chk2 kinase; and, (d) contacting the test compound with the kinase and the polypeptide and measuring the ability of the test compound to inhibit or abrogate phosphorylation of the polypeptide by the kinase. The method can further comprising providing a full length human Cdc25C. In one embodiment of the method, the polypeptide of step (c) comprises amino acid residue serine 216 of human Cdc25C, such as comprising from about amino acid residue 200 to about amino acid residue 250 of human Cdc25C. In one embodiment of the method, the polypeptide of step (c) further comprises glutathione-S-transferase.

In one embodiment of the methods of the invention, including the screening methods, the polypeptide of the invention is immobilized.

The invention provides a method for screening for compounds capable of

checkpoint impaired cell; (c) contacting the cell of step (b) with the test compound or the

polypeptide of step (a) plus a DNA damaging treatment, such as 5-fluorouracil (5-FU), rebeccamycin, adriamycin, bleomycin, cisplatin, hyperthermia, UV irradiation or gamma-irradiation, or, or an M phase checkpoint activator; and, (d) measuring the amount of DNA in the cells after the contacting of step (c) to determine if the test compound has inhibited the G2 cell cycle checkpoint, wherein the polypeptide of step (a) acts as a G2-checkpoint-inhibiting positive control. In alternative embodiments the cell is a mammalian cell, a human cell or a cancer cell. In one embodiment, the amount of DNA is measured using propidium iodide by, e.g., a FACS analysis, or equivalent. In one embodiment, the amount of DNA is measured after about 10 to about 72 hours after the contacting of step (c).

In one embodiment, the method comprises contacting the cell of step (b) with an M phase checkpoint activator alone (as a substitute for a DNA damaging agent) and the test compound or the polypeptide of step (a), wherein a test compound that has not inhibited or abrogated the arrest at the M phase checkpoint of the cell cycle after contacting the cell with an M phase activator is a specific inhibitor of the G2 cell cycle checkpoint (because it did not affect M phase checkpoint or it was not a non-specific phenomenon). In one embodiment, the M phase checkpoint activator is colchicine or nocodazole.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

All publications, patents, patent applications, GenBank sequences and ATCC deposits, cited herein are hereby expressly incorporated by reference for all purposes.

DESCRIPTION OF DRAWINGS

Figure 1 shows chimeric peptides used in and results of experiments demonstrating that TAT-S216A and TAT-S216 peptides inhibit hChk1 and Chk2/HuCds1 kinase activity *in vitro*, as described in Example 1, below. Figure 1A shows a schematic diagram of the fusion chimeric peptides TAT-control (SEQ ID NO: 1934), TAT-S216A (SEQ ID NO: 1933) and TAT-S216 (SEQ ID NO: 1932). Figure 1B shows SDS-PAGE autoradiograms

Cdc25C (SEQ ID NO:1) were used as a substrate at a concentration of 1 μM. Figure 1C

shows SDS-PAGE autoradiograms demonstrating the results of *in vitro* Cdc25C phosphorylation assays using TAT-S216A peptide to inhibit purified hChk1 and Chk2 HuCds1 activity; amino acid residues 211 to 220 of Cdc25C (SEQ ID NO:1) were used as a substrate at a concentration of 10 μM.

Figure 2 the results of experiments demonstrating that TAT-S216A and TAT-S216 peptides can abrogate DNA damage-induced G2 arrest in Jurkat cells. Figure 2A shows the results of a FACS analysis of Jurkat cells treated with bleomycin (10 μg/ml) and TAT-S216A and TAT-S216 peptides (10 μM each). Figure 2B shows the results of an SDS-PAGE of cell lysates from a histone H1 kinase analysis; lysates were prepared from cells treated with the indicated reagent for six hours. Figure 2C shows the results a FACS analysis of colchicines- (5 μg/ml) and peptide- (10 μM each) treated cells; Jurkat cells were treated for 20 hours.

Figure 3 shows the results of experiments demonstrating that TAT-S216A and TAT-S216 peptides can specifically sensitize cancer cells to bleomycin, but not colchicine. Figure 3A shows the results of trypan blue dye exclusion analysis of Jurkat cells treated with bleomycin with or without the TAT-S216A and TAT-S216 peptides. Figure 3B shows the results of trypan blue dye exclusion (survival) analysis of Jurkat cells treated with colchicine with or without the TAT-S216A and TAT-S216 peptides. Figure 3C shows the results of trypan blue dye exclusion (survival) analysis of PHA blasts treated with bleomycin with or without the TAT-S216A and TAT-S216 peptides. Figure 3D shows the results of FACS analysis PHA blasts treated with bleomycin with or without the TAT-S216A and TAT-S216 peptides (vertical axis is DNA content indicated by propidium iodide staining).

Figure 4 shows the results of experiments demonstrating that TAT-S216A and TAT-S216 peptides can sensitize cancer cells to bleomycin. Figure 4A shows the results of X-TT analysis of PANC1 cells treated with bleomycin with or without the TAT-S216A and TAT-S216 peptides. Figure 4B shows the results of X-TT analysis of MIA PaCa2 cells treated with bleomycin with or without the TAT-S216A and TAT-S216 peptides.

Figure 5 shows a schematic 3-dimensional structure of human Chk2

Figure 6 shows the results of FACS analysis of the amount of DNA in cells to determine the number of cells in one of the four cell cycle phases after incubating these cells with bleomycin and exemplary peptides of the invention, as described in Example 3, below.

Figure 7 shows the results of FACS analysis of the amount of DNA in cells to determine the number of cells in one of the four cell cycle phases after incubating these cells with colchicine and exemplary peptides of the invention, as described in Example 3, below.

Figure 8 shows the sequences of peptides (SEQ ID NOS 1935-1948) used in experiments described in Example 4, below.

Figure 9 shows a summary of results of experiments as described in Example 4, below.

Figure 10 shows the results of experiments demonstrating that a peptide of the invention (as a S216-containing fusion protein) administered to an animal *in vivo* effectively sensitized cancer cells to a DNA damaging agent.

Figure 11 shows the results of experiments demonstrating that a peptide of the invention (as a R-II-containing fusion protein) administered to an animal *in vivo* effectively sensitized cancer cells to a DNA damaging agent.

Like reference symbols in the various drawings indicate like elements.

DETAILED DESCRIPTION

The genes and polypeptides of the invention provide a novel means to treat cell proliferative disorders, including, e.g., to stop the growth of, or kill, cancer cells. While the invention is not limited by any particular mechanism of action, administration of the polypeptides of the invention will delay or abrogate G2 cell cycle arrest checkpoint in cells. The genes and polypeptides of the invention can also be used to inhibit Chk1 and/or Chk2/Cds1 kinase activity. Inhibition of Chk1 and/or Chk2/Cds1 kinase may be the mechanism by which the G2 checkpoint is inhibited. The invention also provides methods for selectively sensitizing G1 checkpoint impaired cancer cells to DNA damaging agents and treatments. Also provided are methods for screening for compounds able to interact with,

The amino acid sequence of human Chk2 kinase is

MSRESDVEAQQSHGSSACSQPHGSVTQSQGSSSQSQGISSSSTS
MPNSSQSSHSSSGTLSSLETVSTQELYSIPEDQEPEDQEPEEPTPAPWARLWALQDG
FANLECVNDNYWFGRDKSCEYCFDEPLLKRTDKYRTYSKKHFRIFREVGPKNSYIAYI
EDHSGNGTFVNTELVGKGKRRPLNNNSEIALSLSRNKVFVFFDLTVDDQSVYPKALRD
EYIMSKTLGSGACGEVKLAFERKTCKKVAIKIISKRKFAIGSAREADPALNVETEIEI
LKKLNHPCIIKIKNFFDAEDYYIVLELMEGGELFDKVVGNKRLKEATCKLYFYQMLLA
VQYLHENGIIHRDLKPENVLLSSQEEDCLIKITDFGHSKILGETSLMRTLCGTPTYLA
PEVLVSVGTAGYNRAVDCWSLGVILFICLSGYPPFSEHRTQVSLKDQITSGKYNFIPE
VWAEVSEKALDLVKKLLVVDPKARFTTEEALRHPWLQDEDMKRKFQDLLSEENESTAL
PQVLAQPSTSRKRPREGEAEGAETTKRPAVCAAVL (SEQ ID NO: 4 1903)

See also Brown (1999) Proc. Natl. Acad. Sci. USA 96:3745-3750; Chaturvedi (1999) Oncogene 18:4047-4054; Genbank Accession Nos. NP 009125; NM 007194.

Antibody Generation

The invention provides antibodies that specifically bind to the peptides and polypeptides of the invention. These antibodies can be used to identify the presence of these peptides and polypeptides. The peptides and polypeptides of the invention can be used as immunogens to generate antibodies specific for a corresponding Cdc25C phosphatase. The anti-peptide antibodies of the invention can be used to generate anti-idiotype antibodies that specifically bind to active sites of Chk1 or Chk2 kinase.

Methods of producing polyclonal and monoclonal antibodies are known to those of skill in the art and described in the scientific and patent literature, see, *e.g.*, Coligan, CURRENT PROTOCOLS IN IMMUNOLOGY, Wiley/Greene, NY (1991); Stites (eds.) BASIC AND CLINICAL IMMUNOLOGY (7th ed.) Lange Medical Publications, Los Altos, CA ("Stites"); Goding, MONOCLONAL ANTIBODIES: PRINCIPLES AND PRACTICE (2d ed.) Academic Press, New York, NY (1986); Kohler (1975) Nature 256:495; Harlow (1988) ANTIBODIES, A LABORATORY MANUAL, Cold Spring Harbor Publications, New York. Antibodies can be generated *in vitro*, *e.g.*, using recombinant antibody binding site expressing phage display libraries, in addition to the traditional *in vivo* methods using animals. See, *e.g.*, Huse (1989) Science 246:1275; Ward (1989) Nature 341:544; Hoogenboom (1997) Trends Biotechnol. 15:62-70; Katz (1997) Annu. Rev. Biophys. Biomol. Struct. 26:27-45. Human antibodies can be generated in mice engineered to produce only human antibodies, as described by, e.g.,

line such as a myeloma or by manipulating such B-cells by other techniques to perpetuate a

cell line) to produce a monoclonal human antibody-producing cell. See, e.g., U.S. Patent No. 5,916,771; 5,985,615. For making chimeric, *e.g.*, "humanized," antibodies, see *e.g.*, U.S. Patent Nos. 5,811,522; 5,789,554; 5,861,155. Alternatively, recombinant antibodies can also be expressed by transient or stable expression vectors in mammalian, including human, cells as in Norderhaug (1997) J. Immunol. Methods 204:77-87; Boder (1997) Nat. Biotechnol. 15:553-557; see also U.S. Patent No. 5,976,833

Screening for candidate compounds

The invention provides compositions and methods for screening for potential therapeutic compounds ("candidate compounds") to inhibit or abrogate Chk1 and/or Chk2/Cds1 kinase activity and/or the G2 cell cycle arrest checkpoint. For example, the screening can involve *in vitro* or *in vivo* assays wherein Chk1 and Chk2/Cds1 kinases phosphorylate peptides and polypeptides comprising the motifs of the invention; see Example 1, below. Inhibitors of peptide phosphorylation are candidate compounds. Alternatively, assays incorporating the experiments, or variations thereof, as set forth in Example 1, below, can be designed to assay for candidate compounds which can inhibit or abrogate Chk1 and/or Chk2/Cds1 kinase activity and/or the G2 cell cycle arrest checkpoint.

In one embodiment, the peptides and polypeptides of the invention can be bound to a solid support. Solid supports can include, e.g., membranes (e.g., nitrocellulose or nylon), a microtiter dish (e.g., PVC, polypropylene, or polystyrene), a test tube (glass or plastic), a dip stick (e.g., glass, PVC, polypropylene, polystyrene, latex and the like), a microfuge tube, or a glass, silica, plastic, metallic or polymer bead or other substrate such as paper. One solid support uses a metal (e.g., cobalt or nickel)-comprising column which binds with specificity to a histidine tag engineered onto a peptide.

Adhesion of peptides to a solid support can be direct (i.e. the protein contacts the solid support) or indirect (a particular compound or compounds are bound to the support and the target protein binds to this compound rather than the solid support). Peptides can be immobilized either covalently (e.g., utilizing single reactive thiol groups of cysteine residues [illegible] Collins J (1993) Bioconjugate Chem. 4:528-536) [illegible] Biophys. Biochem. Res. Comm. 230:76-80); metal chelating, e.g., Langmuir-Blodgett films (see, e.g.,

Ng (1995) Langmuir 11:4048-55); metal-chelating self-assembled monolayers (see, e.g., Sigal (1996) Anal. Chem. 68:490-497) for binding of polyhistidine fusions.

Indirect binding can be achieved using a variety of linkers which are commercially available. The reactive ends can be any of a variety of functionalities including, but not limited to: amino reacting ends such as N-hydroxysuccinimide (NHS) active esters, imidoesters, aldehydes, epoxides, sulfonyl halides, isocyanate, isothiocyanate, and nitroaryl halides; and thiol reacting ends such as pyridyl disulfides, maleimides, thiophthalimides, and active halogens. The heterobifunctional crosslinking reagents have two different reactive ends, e.g., an amino-reactive end and a thiol-reactive end, while homobifunctional reagents have two similar reactive ends, e.g., bismaleimidohexane (BMH) which permits the cross-linking of sulfhydryl-containing compounds. The spacer can be of varying length and be aliphatic or aromatic. Examples of commercially available homobifunctional cross-linking reagents include, but are not limited to, the imidoesters such as dimethyl adipimidate dihydrochloride (DMA); dimethyl pimelimidate dihydrochloride (DMP); and dimethyl suberimidate dihydrochloride (DMS). Heterobifunctional reagents include commercially available active halogen-NHS active esters coupling agents such as N-succinimidyl bromoacetate and N-succinimidyl (4-iodoacetyl)aminobenzoate (SIAB) and the sulfosuccinimidyl derivatives such as sulfosuccinimidyl(4-iodoacetyl)aminobenzoate (sulfo-SIAB) (Pierce). Another group of coupling agents is the heterobifunctional and thiol cleavable agents such as N-succinimidyl 3-(2-pyridyidithio)propionate (SPDP) (Pierce Chemicals, Rockford, IL).

Antibodies can be used for binding polypeptides and peptides of the invention to a solid support. This can be done directly by binding peptide-specific antibodies to the column or it can be done by creating fusion protein chimeras comprising motif-containing peptides linked to, e.g., a known epitope (e.g., a tag (e.g., FLAG, myc) or an appropriate immunoglobulin constant domain sequence (an "immunoadhesin," see, e.g., Capon (1989) Nature 377:525-531 (1989).

There are a variety of assay formats that can be used to screen for "candidate

phosphorylation of the motif-comprising peptides of the invention can be candidate

compounds. Alternatively, compounds that specifically bind to the motifs of the invention can be candidate compounds. For a general description of different formats for binding assays, see, e.g., BASIC AND CLINICAL IMMUNOLOGY, 7th Ed. (D. Stiles and A. Terr, ed.)(1991); ENZYME IMMUNOASSAY, E.T. Maggio, ed., CRC Press, Boca Raton, Florida (1980); and "Practice and Theory of Enzyme Immunoassays" in P. Tijssen, LABORATORY TECHNIQUES IN BIOCHEMISTRY AND MOLECULAR BIOLOGY, Elsevier Science Publishers, B.V. Amsterdam (1985).

Combinatorial chemical libraries

Combinatorial chemical libraries are one means to assist in the generation of new chemical compound leads, i.e., compounds that inhibit Chk1 and/or Chk2/Cds1 kinase and/or inhibit or abrogate the G2 cell cycle arrest checkpoint. A combinatorial chemical library is a collection of diverse chemical compounds generated by either chemical synthesis or biological synthesis by combining a number of chemical "building blocks" such as reagents. For example, a linear combinatorial chemical library such as a polypeptide library is formed by combining a set of chemical building blocks called amino acids in every possible way for a given compound length (i.e., the number of amino acids in a polypeptide compound). Millions of chemical compounds can be synthesized through such combinatorial mixing of chemical building blocks. For example, the systematic, combinatorial mixing of 100 interchangeable chemical building blocks results in the theoretical synthesis of 100 million tetrameric compounds or 10 billion pentameric compounds (see, e.g., Gallop et al. (1994) 37(9): 1233-1250). Preparation and screening of combinatorial chemical libraries are well known to those of skill in the art, see, e.g., U.S. Patent No. 6,004,617; 5,985,356. Such combinatorial chemical libraries include, but are not limited to, peptide libraries (see, e.g., U.S. Patent No. 5,010,175; Furka (1991) Int. J. Pept. Prot. Res., 37: 487-493, Houghton et al. (1991) Nature, 354: 84-88). Other chemistries for generating chemical diversity libraries include, but are not limited to: peptoids (see, e.g., WO 91/19735), encoded peptides (see, e.g., WO 93/20242), random bio-oligomers (see, e.g., WO 92/00091), benzodiazepines (see, e.g., U.S. Patent No. 5,288,514), diversomers such as hydantoins, benzodiazepines and

[illegible] peptidomimetics with a Beta- D- Glucose scaffolding (see, e.g., Hirschmann (1992) J. Amer.

Chem. Soc. 114: 9217-9218), analogous organic syntheses of small compound libraries (see, e.g., Chen (1994) J. Amer. Chem. Soc. 116: 2661), oligocarbamates (see, e.g., Cho (1993) Science 261:1303), and/or peptidyl phosphonates (see, e.g., Campbell (1994) J. Org. Chem. 59: 658). See also Gordon (1994) J. Med. Chem. 37:1385; for nucleic acid libraries, peptide nucleic acid libraries, see, e.g., U.S. Patent No. 5,539,083; for antibody libraries, see, e.g., Vaughn (1996) Nature Biotechnology 14:309-314; for carbohydrate libraries, see, e.g., Liang et al. (1996) Science 274: 1520-1522, U.S. Patent No. 5,593,853; for small organic molecule libraries, see, e.g., for isoprenoids U.S. Patent 5,569,588; for thiazolidinones and metathiazanones, U.S. Patent No. 5,549,974; for pyrrolidines, U.S. Patent Nos. 5,525,735 and 5,519,134; for morpholino compounds, U.S. Patent No. 5,506,337; for benzodiazepines U.S. Patent No. 5,288,514.

Devices for the preparation of combinatorial libraries are commercially available (see, e.g., U.S. Patent No. 6,045,755; 5,792,431 ; 357 MPS, 390 MPS, Advanced Chem Tech, Louisville KY, Symphony, Rainin, Woburn, MA, 433A Applied Biosystems, Foster City, CA, 9050 Plus, Millipore, Bedford, MA). A number of robotic systems have also been developed for solution phase chemistries. These systems include automated workstations, e.g., like the automated synthesis apparatus developed by Takeda Chemical Industries, LTD. (Osaka, Japan) and many robotic systems utilizing robotic arms (Zymate II, Zymark Corporation, Hopkinton, Mass.; Orca, Hewlett-Packard, Palo Alto, Calif.) which mimic the manual synthetic operations performed by a chemist. Any of the above devices are suitable for use with the present invention. The nature and implementation of modifications to these devices (if any) so that they can operate as discussed herein will be apparent to persons skilled in the relevant art. In addition, numerous combinatorial libraries are themselves commercially available (see, e.g., ComGenex, Princeton, N.J., Asinex, Moscow, Ru, Tripos, Inc., St. Louis, MO, ChemStar, Ltd, Moscow, RU, 3D Pharmaceuticals, Exton, PA, Martek Biosciences, Columbia, MD, etc.).

Formulation and Administration of Pharmaceutical Compositions

In one embodiment, the peptides and polypeptides of the invention are combined with a pharmaceutically acceptable carrier (excipient) to form a pharmacological composition. Pharmaceutically acceptable carriers can contain a physiologically acceptable compound that acts to, e.g., stabilize, or increase or decrease the absorption or clearance rates of the pharmaceutical compositions of the invention. Physiologically acceptable compounds can include, e.g., carbohydrates, such as glucose, sucrose, or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins, compositions that reduce the clearance or hydrolysis of the peptides or polypeptides, or excipients or other stabilizers and/or buffers. Detergents can also used to stabilize or to increase or decrease the absorption of the pharmaceutical composition, including liposomal carriers. Pharmaceutically acceptable carriers and formulations for peptides and polypeptide are known to the skilled artisan and are described in detail in the scientific and patent literature, see e.g., the latest edition of Remington's Pharmaceutical Science, Mack Publishing Company, Easton, Pennsylvania ("Remington's").

Other physiologically acceptable compounds include wetting agents, emulsifying agents, dispersing agents or preservatives which are particularly useful for preventing the growth or action of microorganisms. Various preservatives are well known and include, e.g., phenol and ascorbic acid. One skilled in the art would appreciate that the choice of a pharmaceutically acceptable carrier including a physiologically acceptable compound depends, for example, on the route of administration of the peptide or polypeptide of the invention and on its particular physio-chemical characteristics.

In one embodiment, a solution of peptide or polypeptide of the invention is dissolved in a pharmaceutically acceptable carrier, e.g., an aqueous carrier if the composition is water-soluble. Examples of aqueous solutions that can be used in formulations for enteral, parenteral or transmucosal drug delivery include, e.g., water, saline, phosphate buffered saline, Hank's solution, Ringer's solution, dextrose saline, glucose solutions and the like. The formulations can contain pharmaceutically acceptable auxiliary substances as required to

[illegible]

ingredients such as bactericidal agents, or stabilizers. For example, the solution can contain

sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate or triethanolamine oleate. These compositions can be sterilized by conventional, well-known sterilization techniques, or can be sterile filtered. The resulting aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous solution prior to administration. The concentration of peptide in these formulations can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight and the like in accordance with the particular mode of administration selected and the patient's needs.

Solid formulations can be used for enteral (oral) administration. They can be formulated as, e.g., pills, tablets, powders or capsules. For solid compositions, conventional nontoxic solid carriers can be used which include, e.g., pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. For oral administration, a pharmaceutically acceptable nontoxic composition is formed by incorporating any of the normally employed excipients, such as those carriers previously listed, and generally 10% to 95% of active ingredient (e.g., peptide). A non-solid formulation can also be used for enteral administration. The carrier can be selected from various oils including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like. Suitable pharmaceutical excipients include e.g., starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol.

Peptides and polypeptides of the invention, when administered orally, can be protected from digestion. This can be accomplished either by complexing the peptide or polypeptide with a composition to render it resistant to acidic and enzymatic hydrolysis or by packaging the peptide or complex in an appropriately resistant carrier such as a liposome. Means of protecting compounds from digestion are well known in the art, see, e.g., Fix (1996) Pharm Res. 13:1760-1764; Samanen (1996) J. Pharm. Pharmacol. 48:119-135; U.S. Patent 5,391,377, describing lipid compositions for oral delivery of therapeutic agents

For transmucosal or transdermal administration, penetrants appropriate to the barrier to be

permeated can be used in the formulation. Such penetrants are generally known in the art, and include, e.g., for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents can be used to facilitate permeation. Transmucosal administration can be through nasal sprays or using suppositories. See, e.g., Sayani (1996) "Systemic delivery of peptides and proteins across absorptive mucosae" Crit. Rev. Ther. Drug Carrier Syst. 13:85-184. For topical, transdermal administration, the agents are formulated into ointments, creams, salves, powders and gels. Transdermal delivery systems can also include, e.g., patches.

The peptides and polypeptide complexes can also be administered in sustained delivery or sustained release mechanisms, which can deliver the formulation internally. For example, biodegradeable microspheres or capsules or other biodegradeable polymer configurations capable of sustained delivery of a peptide can be included in the formulations of the invention (see, e.g., Putney (1998) Nat. Biotechnol. 16:153-157).

For inhalation, the peptide or polypeptide can be delivered using any system known in the art, including dry powder aerosols, liquids delivery systems, air jet nebulizers, propellant systems, and the like. See, e.g., Patton (1998) Biotechniques 16:141-143; product and inhalation delivery systems for polypeptide macromolecules by, e.g., Dura Pharmaceuticals (San Diego, CA) , Aradigm (Hayward, CA), Aerogen (Santa Clara, CA), Inhale Therapeutic Systems (San Carlos, CA), and the like. For example, the pharmaceutical formulation can be administered in the form of an aerosol or mist. For aerosol administration, the formulation can be supplied in finely divided form along with a surfactant and propellant. In another embodiment, the device for delivering the formulation to respiratory tissue is an inhaler in which the formulation vaporizes. Other liquid delivery systems include, e.g., air jet nebulizers.

In preparing pharmaceuticals of the present invention, a variety of formulation modifications can be used and manipulated to alter pharmacokinetics and biodistribution. A number of methods for altering pharmacokinetics and biodistribution are known to one of ordinary skill in the art. Examples of such methods include protection of the complexes in

pharmacokinetics, see, e.g., Remington's, Chapters 37-39.

The peptide and polypeptide complexes used in the methods of the invention can be delivered alone or as pharmaceutical compositions by any means known in the art, e.g., systemically, regionally, or locally (e.g., directly into, or directed to, a tumor); by intraarterial, intrathecal (IT), intravenous (IV), parenteral, intra-pleural cavity, topical, oral, or local administration, as subcutaneous, intra-tracheal (e.g., by aerosol) or transmucosal (e.g., buccal, bladder, vaginal, uterine, rectal, nasal mucosa). Actual methods for preparing administrable compositions will be known or apparent to those skilled in the art and are described in detail in the scientific and patent literature, see e.g., Remington's. For a "regional effect," e.g., to focus on a specific organ, one mode of administration includes intra-arterial or intrathecal (IT) injections, e.g., to focus on a specific organ, e.g., brain and CNS (see e.g., Gurun (1997) Anesth Analg. 85:317-323). For example, intra-carotid artery injection if preferred where it is desired to deliver a peptide or polypeptide complex of the invention directly to the brain. Parenteral administration is a preferred route of delivery if a high systemic dosage is needed. Actual methods for preparing parenterally administrable compositions will be known or apparent to those skilled in the art and are described in detail, in e.g., Remington's,. See also, Bai (1997) J. Neuroimmunol. 80:65-75; Warren (1997) J. Neurol. Sci. 152:31-38; Tonegawa (1997) J. Exp. Med. 186:507-515.

In one embodiment, the pharmaceutical formulations comprising peptides or polypeptides of the invention are incorporated in lipid monolayers or bilayers, e.g., liposomes, see, e.g., U.S. Patent No. 6,110,490; 6,096,716; 5,283,185; 5,279,833. The invention also provides formulations in which water soluble peptides or complexes have been attached to the surface of the monolayer or bilayer. For example, peptides can be attached to hydrazide- PEG- (distearoylphosphatidyl) ethanolamine- containing liposomes (see, e.g., Zalipsky (1995) Bioconjug. Chem. 6:705-708). Liposomes or any form of lipid membrane, such as planar lipid membranes or the cell membrane of an intact cell, e.g., a red blood cell, can be used. Liposomal formulations can be by any means, including administration intravenously, transdermally (see, e.g., Vutla (1996) J. Pharm. Sci. 85:5-8), transmucosally, or orally. The invention also provides pharmaceutical preparations in which the peptides

Liposomes and liposomal formulations can be prepared according to standard methods and

are also well known in the art, see, e.g., Remington's; Akimaru (1995) Cytokines Mol. Ther. 1:197-210; Alving (1995) Immunol. Rev. 145:5-31; Szoka (1980) Ann. Rev. Biophys. Bioeng. 9:467, U.S. Pat. Nos. 4, 235,871, 4,501,728 and 4,837,028.

Treatment Regimens: Pharmacokinetics

The pharmaceutical compositions can be administered in a variety of unit dosage forms depending upon the method of administration. Dosages for typical peptide and polypeptide pharmaceutical compositions are well known to those of skill in the art. Such dosages are typically advisorial in nature and are adjusted depending on the particular therapeutic context, patient tolerance, etc. The amount of peptide or polypeptide adequate to accomplish this is defined as a "therapeutically effective dose." The dosage schedule and amounts effective for this use, i.e., the "dosing regimen," will depend upon a variety of factors, including the stage of the disease or condition, the severity of the disease or condition, the general state of the patient's health, the patient's physical status, age, pharmaceutical formulation and concentration of active agent, and the like. In calculating the dosage regimen for a patient, the mode of administration also is taken into consideration. The dosage regimen must also take into consideration the pharmacokinetics, i.e., the pharmaceutical composition's rate of absorption, bioavailability, metabolism, clearance, and the like. See, e.g., the latest Remington's; Egleton (1997) "Bioavailability and transport of peptides and peptide drugs into the brain" Peptides 18:1431-1439; Langer (1990) Science 249:1527-1533.

In therapeutic applications, compositions are administered to a patient suffering from a cancer in an amount sufficient to at least partially arrest the disease and/or its complications. For example, in one embodiment, a soluble peptide pharmaceutical composition dosage for intravenous (IV) administration would be about 0.01 mg/hr to about 1.0 mg/hr administered over several hours (typically 1, 3, or 6 hours), which can be repeated for weeks with intermittent cycles. Considerably higher dosages (e.g., ranging up to about 10 mg/ml) can be used, particularly when the drug is administered to a secluded site and not into the blood stream, such as into a body cavity or into a lumen of an organ, e.g., the

EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention.

Example 1: Administration of peptides of the invention to selectively sensitize cancer cells to DNA damaging agents

The invention provides compositions and methods for sensitizing cells, particularly cells with an impaired G1 cell cycle arrest checkpoint, such as cancer cells, to DNA damaging agents. The following example describes studies which demonstrate that the compositions and methods of the invention are effective for selectively killing cancer cells (versus normal cells, which have an unimpaired G1 checkpoint). Specifically, these experiments describes the synthesis and use of two exemplary polypeptides of the invention. Two peptides corresponding to amino acids 211 to 221 of human Cdc25C (SEQ ID NO:1) fused with a part of HIV-1-TAT (SEQ ID NO:5). These peptides were demonstrated to inhibit hChk1 kinase (SEQ ID NO:3) and Chk2/HuCds1 (SEQ ID NO:4) kinase activity *in vitro* and to specifically abrogate the G2 checkpoint *in vivo*.

Chemicals and reagents. Bleomycin and colchicine were purchased from Wako Pure Chemical Co. (Osaka, Japan). Hydroxyurea was purchased from Sigma Chemical Co. (St. Louis, MO). These chemicals were dissolved in distilled H_2O to 10, 5 and 50 mg/ml, respectively, and stored at 4°C. Antibodies against 14-3-3β were purchased from Santa Cruz Biotechnology (Santa Cruz, CA) and anti-rabbit IgG horseradish peroxidase-conjugated secondary antibodies were purchased from Amersham Life Sciences (Arlington Heights, IL). Antibodies against HA and c-myc, and protein G-Sepharose were purchased from Santa Cruz Biotechnology and Amersham Pharmacia Biotech (Uppsala, Sweden), respectively.

Cell culture and plasmids. A human T-cell leukemia-derived cell line, Jurkat, was cultured in RPMI 1640 (Sigma) supplemented with 10% fetal calf serum (IBL: Immuno-Biological Laboratories, Gunma, Japan) at 37°C/5% CO_2. Human pancreatic epitheloid carcinoma-derived cell lines, MIA PaCa2 and PANC1, were cultured in Eagle's MEM

respectively, and supplemented with 10% fetal calf serum at 37°C/5% CO_2. Normal human

peripheral blood lymphocytes were collected by Ficoll-Paque (Amersham Pharmacia Biotech) density gradient. Two million cells/ml were cultured in RPMI 1640 supplemented with 10% fetal calf serum at 37°C/5% CO_2 in the presence of 5 μg/ml PHA (Life Technologies, Inc.) for a week. Baculovirus lysates that include HA-tagged hChk1 (SEQ ID NO:3) or c-myc-tagged Chk2/HuCds1 (SEQ ID NO:4) and plasmid for GST-Cdc25C (amino acid 200-256) were made as described in Matsuoka (1998) Science 282:1893-1897, and provided by Dr. Makoto Nakanishi (Department of Biochemistry, Nagoya City University.

Peptides. TAT-S216 peptide was synthesized so that it contained an NH_2-terminal 11 amino acid TAT protein transduction domain (YGRKKRRQRRR (SEQ ID NO:~~5~~ 1899); see, e.g., Nagahara (1998) Nature Med. 4:1449-1452) followed by a corresponding amino acid 211 to 221 derived from the human Cdc25C amino acid sequence (SEQ ID NO:~~1~~ 1904) (S216; LYRSPASMPENL). Serine-216 residue was changed to alanine in TAT-S216A (S216A; LYRSPSMPENL) (SEQ ID NO:~~6~~ 2). The Cdc25C portion was partially deleted and substituted with glycine in TAT-Control (GGRSPAMPE) (SEQ ID NO:~~7~~ 1905). All peptides were synthesized by Sawady Technology Co. (Tokyo, Japan).

Purification of recombinant GST-Cdc25C proteins. *Escherichia coli* DH5α cells were transformed by GST-Cdc25C (200-256) plasmid. The cells were incubated with 0.1 mM isopropyl β-D-thiogalactoside for 2 hr, harvested, and lysed with a buffer containing 50 mM Tris HCl (pH8.0), 100 mM NaCl, 0.5% NP-40, 5 μg/ml aprotinin, 5 μg/ml pepstatin A and 5 μg/ml leupeptin. The lysate was sonicated, centrifuged for clarification and incubated with glutathione-Sepharose 4B™ beads for 1 hr at 4°C and washed five times.

Kinase assay. HA-tagged hChk1 (SEQ ID NO:3) and c-myc-tagged Chk2/HuCds1 (SEQ ID NO:4) expressed in insect cells using recombinant baculovirus (see, e.g., Kaneko (1999) Oncogene 18:3673-3681) were purified by immunoprecipitation using anti-HA or anti-c-myc antibodies and protein G-Sepharose. Immune complex kinase reaction was done in PBS with 1 mM DTT, 1 mM MgCl2 and 100 μCi of [γ-^{32}P] ATP (Amersham; 6000Ci/mmol) plus purified 1 μM GST-Cdc25C or 10 μM Cdc25C peptide (amino acid 211 to 221 of Cdc25C (SEQ ID NO:~~4~~ 2); LYRSPSMPENL, Sawady Technology

autoradiographed to detect GST-Cdc25C or peptide phosphorylation.

Cell-cycle analysis. The cell cycle status of the cells treated with peptides and/or bleomycin or colchicine was analyzed by FACS, as described by Kawabe (1997) Nature 385:454-458. In brief, two million Jurkat cells were re-suspended and incubated in 300 µl Krishan's solution (0.1% Sodium citrate, 50 µg/ml PI, 20 µg/ml RNase A and 0.5% NP-40; see supra) for 1 hr at 4°C and analyzed by FACScan™ (Beckton Dickinson, Mountain View, CA) with the program CELLQuest™ (Beckton Dickinson).

Histone H1 kinase assay. Ten million Jurkat cells were treated with hydroxyurea (100 µg/ml), bleomycin (10 µg/ml), or colchicine (5 µg/ml) with or without addition of TAT-S216A, TAT-S216 or TAT-Control (10 µM) for 6 hr. The cells were washed in cold PBS and lysed at 4°C in 1 ml of buffer A (50 mM Tris pH 8, 2 mM DTT, 5 mM EDTA, 100 mMNaCl, 0.5% NP40, 20 mM Na_3V0_4, 50 mM NaF, 4 µM Okadaic acid, 5 µg/ml aprotinin, 5 µg/ml pepstatin A and 5 µg/ml leupeptin.). Twenty microliter of $p13^{suc1}$ agarose beads (Upstate Biotechnology., Saranac, NY) were added to the cleared lysates, incubated for 4 hr at 4°C, and washed five times with buffer A without 5 mM EDTA, 20 mM Na_3V0_4, 50 mM NaF, 4 µM Okadaic acid. Histone H1 kinase activity on the beads were analyzed by using Cdc2 kinase assay kit (Upstate Biotechnology) with [γ -^{32}P] ATP followed by 12% SDS-PAGE electrophoresis, and autoradiographed to detect the phosphorylated Histone H1.

Cell cytotoxicity assay. MIA PaCa2 and PANC1 cells ($3x10^3$/well) were plated in 96-well microtiter plates. After an overnight adherence, cells were treated with bleomycin (10 µg/ml) with or without the indicated TAT-peptides at various time points up to 96 hr. Cytotoxicity and cell survival were determined by the 3'-[1-(phenylaminocarbonyl)-3,4-tetrazolium]-bis (4-methoxy-6-nitro) benzene sulfonic acid hydrate) (XTT) assay (Cell Proliferation Kit II™; Boehringer Mannheim, Germany), which was done according to company's protocol and Scudiero (1988) Cancer Res. 48.4827-4833.

TAT-S216 and TAT-S216A peptides inhibit hChk1 and Chk2/HuCds1 kinase activities

To inhibit hChk1 (SEQ ID NO:3) and Chk2/HuCds1 (SEQ ID NO:4) kinase activities and to abrogate DNA damage-induced-G2 arrest, synthetic peptides comprising amino acid residues 211 to 221 of Cdc25C (SEQ ID NO:1) and a variation of the TAT protein transduction domain (YGRKKRRQRRR (SEQ ID NO:~~5~~ 1899) (TAT-S216) were generated.

The results are shown in Figure 1: TAT-S216A and TAT-S216 peptides inhibit hChk1 and Chk2/HuCds1 kinase activities *in vitro*. Figure 1A. sequences of the peptides. Figure 1B, in vitro phosphorylation analysis using GST-Cdc25C and purified hChk1. GST-Cdc25C (amino acid 200-256) that was produced in E. coli (DH5α) was used as substrate (1 μM). Immune complex kinase reaction was done in the presence of TAT-S216A (10 μM) or TAT-S216 (10 μM). Figure 1C, in vitro phosphorylation analysis of hChk1 and Chk2/HuCds1 using synthesized Cdc25C peptide corresponding amino acid 211-221 of Cdc25C (LYRSPSMPENL (SEQ ID NO: 2)) as a substrate (10 μM).

A TAT-S216A peptide (S216A; LYRSPSMPENL, (SEQ ID NO:~~6~~ 2)), in which serine residue 216 was substituted by alanine was devised to stabilize the transient status of its interaction with hChk1 (SEQ ID NO:3) and Chk2/HuCds1 (SEQ ID NO:4) (Fig. 1A). This TAT peptide was included to efficiently transduce these peptides into cells (see, e.g., Nagahara (1998) supra). This sequence is known to facilitate the uptake of heterologous proteins across the cell membrane. As a control peptide, part of the Cdc25C portion of this peptide was deleted (TAT-Control).

As shown in Fig. 1B, hChk1 (SEQ ID NO:3) was capable of phosphorylating a Cdc25C protein (residues 200-256) (SEQ ID NO:1) fused to GST. Serine-216 on Cdc25C (SEQ ID NO:1) is the major phosphorylation site of this fusion protein *in vivo* (see, e.g., Furnari (1997) Science 277:1495-1497; Sanchez (1997) Science 277:1497-1501; Peng (1997) Science 277:1501-1505).

In Fig. 1B, both TAT-S216 and TAT-S216A inhibited the phosphorylation of Cdc25C by baculovirus-produced hChk1 (SEQ ID NO:3). TAT-S216 but not TAT-S216A

phosphorylation at excess molar ratio if present in great enough quantity. TAT-Control peptide did not inhibit hChk1 kinase activity.

As shown in Fig. 1C, TAT-S216A significantly inhibited phosphorylation of Cdc25C peptide (residues 200-256) (SEQ ID NO:1) mediated by hChk1 (SEQ ID NO:3) and Chk2/HuCds1 (SEQ ID NO:4) even at a low stoichiometry (at four times more molar excess of TAT-S216A peptide against substrate Cdc25C peptide).

Abrogation of DNA damage-induced G2 checkpoint by TAT-S216 and TAT-S216A peptides

The cell cycle status of the cells treated with TAT-S216A or TAT-S216 upon the DNA damage-induced G2 arrest was analyzed by FACS analysis. Histone H1 kinase activities of theses cells were simultaneously monitored. Jurkat cells arrested exclusively at G2 by bleomycin (10 μg/ml) treatment, because it does not have functional p53. Results are shown in Figure 2: abrogation of DNA damage-induced G2 arrest by TAT-S216A and TAT-S216 peptides. Figure 2A, FACS analysis of Jurkat cells treated with bleomycin and peptides. Cells were treated with bleomycin (10 μg/ml) with or without peptides (10 μM) for 20 hr. B, histone H1 kinase analysis. Cell lysates were prepared from the cells treated with the indicated reagent for 6 hr. Concentrations used were: hydroxyurea (HU), 100 μg/ml; bleomycin (Bleo), 10 μg/ml; colchicine, 5 μg/ml; TAT-S216A and TAT-S216, 10 μM. C, FACS analysis of colchicine -and peptide-treated cells. Jurkat cells were treated with colchicine (5 μg/ml) with or without peptide (10 μM) for 20 hr.

As shown in Fig. 2A, G2 arrest was completely abrogated by the addition of TAT-S216A or TAT-S216 in response to bleomycin. G2 arrest was abrogated at any time point between 12 and 48 hr by the treatment with TAT-S216A or TAT-S216. Jurkat cells treated with bleomycin together with TAT-Control arrested at G2 similarly to the cells treated with bleomycin alone.

We also observed that either TAT-S216A or TAT-S216 also abrogated G2 arrest induced by gamma-irradiation and cisplatin (gamma-irradiation, 5 Gy; cisplatin, 1 μg ml for 1 hr treatment). To further analyze the effect of these peptides on G2/M transition,

was unchanged or rather increased by the treatment with bleomycin in the presence of TAT-

S216A or TAT-S216 (Fig. 2B). In the presence of TAT-Control peptide, the bleomycin treatment did not affect with H1 kinase activity.

As shown in Fig. 2C, The M-phase arrest of Jurkat cells induced by colchicine was not affected by the addition of TAT-S216 or TAT-S216A. These results demonstrate that TAT-S216A and TAT-S216 specifically abrogated the DNA damage-activated cell cycle G2 checkpoint by inhibiting hChk1 (SEQ ID NO:3) and/or Chk2/HuCds1 (SEQ ID NO:4) kinase activities.

Sensitization of Jurkat cells to the bleomycin-induced cell death by TAT-S216A and TAT-S216 peptides

The effect of TAT-S216A and TAT-S216 on the cell death induced by bleomycin was examined. The results are shown in Figure 3; Trypan blue dye exclusion analysis of Jurkat cells treated with bleomycin (A) or colchicine (B) with or without indicated peptides. Bars, SD Vertical axis, % viability of the cells; Bleo 5, bleomycin 5 μg/ml; Bleo 10, bleomycin 10 μg/ml; colchicine, 5 μg/ml; TAT-S216 or TAT-S216A, 10 μM of indicated peptide. Note that TAT-S216A and TAT-S216 peptides did not increase the cytotoxicity of bleomycin to normal cells. C, survival analysis of PHA blasts treated with bleomycin and peptides. Vertical axis, % viability of the cells determined by trypan blue dye exclusion analysis; horizontal axis, time in hours. Bleo 5, bleomycin 5 μg/ml; Bleo 10, bleomycin 10 μg/ml; TAT-S216 or TAT-S216A, 10 μM of indicated peptide. D, FACS analysis of the cells treated with bleomycin and peptides. PHA-blasts were treated with bleomycin with or without peptides for 20 hr. Vertical axis, cell number; horizontal axis, DNA content indicated by propidium iodide staining.

As shown in Fig. 3A, the addition of TAT-S216A and TAT-S216 efficiently sensitized Jurkat cells to the bleomycin-induced cell death. Whereas bleomycin treatment at 5 or μ10 g/ml killed Jurkat cells by only 27-30%, the addition of 10 μM TAT-216A or TAT-S216 killed Jurkat cells by nearly 80%. In contrast, these peptide by themselves did not show any significant cytotoxicity. In addition, a control peptide TAT-Control did not affect the viability of bleomycin-treated Jurkat cells. Moreover, as expected from the result in Fig.

bleomycin was not attributable to a nonspecific cytotoxic effect.

TAT-S216 and TAT-S216A peptides did not affect the viability of normal cells

In order to confirm the specificity of the effect of these peptides on cancer cells in which the G1 checkpoint is abrogated, the effect of these peptides on normal human cells was investigated. Mitogen-activated normal human T lymphocytes (PHA blasts) were prepared by stimulating peripheral blood mononuclear cells obtained from a healthy donor with PHA for 1 week. These cells were treated with bleomycin (5 and 10 μ g/ml) in the presence or absence of either TAT-S216A or TAT-S216.

As shown in Fig. 3C, these peptides did not augment the cytotoxic effect of bleomycin, although these cells replicated as fast as Jurkat cells. As shown in Fig. 3D, PHA blasts treated with bleomycin (5 μ g/ml) arrested at G1 and S phase but not G2, presumably because of the activity of wild-type p53. When these cells were treated with TAT-S216 or TAT-S216A in addition to bleomycin, no further alteration of cell cycle pattern was observed.

Sensitization of pancreatic cancer cells to the bleomycin-induced cell death by TAT-S216A and TAT-S216 peptides

The effect of these peptides on two other p53-defective pancreatic cancer cell lines, MIA PaCa2 and PANC1 cells, was examined. Figure 4 shows the results of survival analysis of PANC1 (A) and MIA PaCa2 (B) cells treated with bleomycin and peptides. PANC1 and MIA PaCa2 cells were treated with bleomycin with or without the indicated peptide. The cell viability was determined by the 3'-[1-(phenylaminocarbonyl)-3,4-tetrazolium]-bis (4-methoxy-6-nitro) benzene sulfonic acid hydrate assay at the indicated times after addition of bleomycin and peptide. Bleo 60, bleomycin 60 μg/ml; TAT-S216 or TAT-S216A, 10 μM of indicated peptide. Bars, SD.

Although these pancreatic cancer cells are known to be resistant to various anti-cancer reagents, these cells could also be sensitized to the bleomycin-induced cell death by TAT-S216A and TAT-S216 (Fig. 4). Similarly, these peptides could sensitize these cells to the cell death induced by other DNA-damaging agents including cisplatin and gamma-irradiation.

the DNA damage-induced G2 cell growth arrest checkpoint. These data also demonstrated

that the specific abrogation of the G2 checkpoint sensitized cancer cells to bleomycin, a DNA-damaging agent, without obvious effect on normal cell cycle and its viability. These observations indicate that these kinases involved in G2 cell cycle checkpoint are ideal targets for the specific abrogation of G2 checkpoint and that the peptides and polypeptides of the invention and their derivatives can be used in novel cancer therapy.

Example 2: Optimization of sequences for G2 abrogating peptides of the invention

The following example describes studies which identified exemplary G2 checkpoint-abrogating peptides of the invention. This was accomplished by using a computer analysis of the structure of human Chk2 kinase (SEQ ID NO:4) and the peptides of the invention.

The 3-dimensional structure of human Chk2 was predicted by comparing the primary and 3-D structure of another serine threonine kinase, PKA (PDB protein data base, Research Collaboratory for Structural Bioinformatics (RCSB), The National Science Foundation, Arlington, VA) (1CDK), using a computer program, MODELER™ (IMMD, Tokyo, Japan). The alignment of the peptides of the invention and hChk2 were predicted by comparing an alignment of hChk1 and various Cdc25C peptides as described by Chen (2000) "The 1.7 A crystal structure of human cell cycle checkpoint kinase Chk1: implications for Chk1 regulation," Cell 100:681-92. By comparing the predicted structure of hChk2 with the peptides of the invention, it was predicted that there are four pockets on hChk2 that are important for the interaction with peptides, as shown in Figure 5, P1, P2, P3 and P4. The structure of these pockets was used to design and confirm the sequences of exemplary peptides of the invention

The ability of these peptides to abrogate the activity of Chk2 kinase, thereby imbuing the ability to abrogate the G2 cell cycle checkpoint, was demonstrated by their ability to act as a phosphorylation substrate for human Chk2 kinase. Exemplary peptides were directly synthesized (immobilized) on a membrane and contacted with human Chk2 kinase. Specifically, oligo-peptides with all sequences predicted by the 3-dimensional model were directly synthesized on a membrane by using an auto-spot peptide synthesizer Model

room temperature (RT). Then, they were washed three times with 0.1% Tween-PBS™. The

"kination," or "phosphorylation," reaction was performed with a recombinant fusion protein Gst-Chk2 at a concentration of about 5 μg in 4 ml reaction buffer, 1 mM $MgCl_2$, 2% Gly-Gly and γ-^{33}P-ATP in PBS at RT for 1 hr. After the reaction, the membrane was washed 5 times with RIPA (1% SDS, 1% NP-40, 100 mM NaCl) and analyzed with a Bass 2500™ image analyzer (Fuji, Japan). The signal was graded to "-," a "+," a "++," or a "+++." Table 1 shows the peptide sequences that gave signals stronger than "++." The peptides RYSLPPELSNM (SEQ ID NO: 1) and LYRSPSAMPENL (SEQ ID NO: 1906) gave "+" signals by this analysis.

All of the following peptides were phosphorylated by human Chk2 kinase; in position "X" (corresponding to position X_8), wherein X = P, F, Y, or W, the signal was strongest (a "+++") when X = the amino acid tyrosine (Y):

(SEQ ID NO: 1907) 37-40 L Y R S P S H X E N L
(SEQ ID NO: 1908) 52-53 L Y S S P S Y X E N L
(SEQ ID NO: 1909) 92-95 L Y T S P S Y X E N L
(SEQ ID NO: 1910) 117-121 L Y T S P S H X E N L
(SEQ ID NO: 1911) 132-135 L Y H S P S Y X E N L
(SEQ ID NO: 1912) 1127-1130 W Y R S P S F X E N L
(SEQ ID NO: 1913) 1237-1240 W Y T S P S H X E N L
(SEQ ID NO: 1914) 372-375 L F T S P S Y X E N L
(SEQ ID NO: 1915) 637-640 F Y S S P S H X E N L
(SEQ ID NO: 1916) 642-645 F Y T S P S M X E N L
(SEQ ID NO: 1917) 648-651 F Y T S P S F X E N L
(SEQ ID NO: 1918) 652-655 F Y T S P S Y X E N L
(SEQ ID NO: 1919) 1202-1205 W Y T S P S M X E N L
(SEQ ID NO: 1920) 1207-1210 W Y T S P S F X E N L
(SEQ ID NO: 1921) 1212-1215 W Y T S P S Y X E N L

The best phosphorylation substrates were the peptides L Y R S P S Y Y E N L (SEQ ID NO: [illegible]) and W Y T S P S Y E E N L (SEQ ID NO: [illegible]).

[illegible] phosphorylation by human Chk2 kinase assay. Results are presented to the right of the peptide, below: a "+++" indicates the peptide was relatively highly phosphorylated; a "++"

indicates the peptide was relatively less phosphorylated, a "+" indicates the peptide was detectably significantly phosphorylated over negative control, and no indication indicates that a peptide was not significantly phosphorylated over negative control (note: the number immediately to the right of the peptide is the MW of the peptide).

Table 1

1 R Y S L P P E L S N M 1308.6		**1 R Y S L P P E L S N M 1308.6**
(SEQ ID NO: 1)	+	**(SEQ ID NO: 1)**
2 L Y R S P S M P E N L 1308.6		**2 L Y R S P S M P E N L 1308.6**
(SEQ ID NO: 2)	+	**(SEQ ID NO: 2)**
3 L Y R S P S M F E N L 1358.6	-	(SEQ ID NO: 3)
4 L Y R S P S M Y E N L 1374.6	-	(SEQ ID NO: 4)
5 L Y R S P S M W E N L 1397.7	-	(SEQ ID NO: 5)
7 L Y R S P S F P E N L 1324.5	-	(SEQ ID NO: 6)
8 L Y R S P S F F E N L 1374.5	-	(SEQ ID NO: 7)
9 L Y R S P S F Y E N L 1390.5	-	(SEQ ID NO: 8)
10 L Y R S P S F W E N L 1413.6	-	(SEQ ID NO: 9)
12 L Y R S P S Y P E N L 1340.5	+	(SEQ ID NO: 10)
13 L Y R S P S Y F E N L 1390.5	+	(SEQ ID NO: 11)
14 L Y R S P S Y Y E N L 1406.5	+	(SEQ ID NO: 12)
15 L Y R S P S Y W E N L 1429.6	+	(SEQ ID NO: 13)
17 L Y R S P S D P E N L 1292.4	-	(SEQ ID NO: 14)
18 L Y R S P S D F E N L 1342.4	-	(SEQ ID NO: 15)
19 L Y R S P S D Y E N L 1358.4	-	(SEQ ID NO: 16)
20 L Y R S P S D W E N L 1381.5	-	(SEQ ID NO: 17)
22 L Y R S P S E P E N L 1306.4	-	(SEQ ID NO: 18)
23 L Y R S P S E F E N L 1356.4	-	(SEQ ID NO: 19)
24 L Y R S P S E Y E N L 1372.4	-	(SEQ ID NO: 20)
25 L Y R S P S E W E N L 1395.5	-	(SEQ ID NO: 21)
27 L Y R S P S N P E N L 1291.5	+	(SEQ ID NO: 22)
28 L Y R S P S N F E N L 1341.5	+	(SEQ ID NO: 23)
29 L Y R S P S N Y E N L 1357.5	+	(SEQ ID NO: 24)
30 L Y R S P S N W E N L 1380.6	+	(SEQ ID NO: 25)
[illegible]		[illegible]
35 L Y R S P S Q W E N L 1394.6	-	(SEQ ID NO: 29)

37 L Y R S P S H P E N L 1314.5	(SEQ ID NO: 30)
38 L Y R S P S H F E N L 1364.5	(SEQ ID NO: 31)
39 L Y R S P S H Y E N L 1380.5	(SEQ ID NO: 32)
40 L Y R S P S H W E N L 1403.6	(SEQ ID NO: 33)
42 L Y S S P S M P E N L 1240.3	(SEQ ID NO: 34)
43 L Y S S P S M F E N L 1290.3	(SEQ ID NO: 35)
44 L Y S S P S M Y E N L 1306.3	(SEQ ID NO: 36)
45 L Y S S P S M W E N L 1329.4	(SEQ ID NO: 37)
47 L Y S S P S F P E N L 1256.2 (SEQ ID NO: 38)	(SEQ ID NO: 30)
48 L Y S S P S F F E N L 1306.2 (SEQ ID NO: 39)	(SEQ ID NO: 31)
49 L Y S S P S F Y E N L 1322.2 (SEQ ID NO: 40)	(SEQ ID NO: 32)
50 L Y S S P S F W E N L 1345.3 (SEQ ID NO: 41)	(SEQ ID NO: 33)
52 L Y S S P S Y P E N L 1272.2 (SEQ ID NO: 42)	(SEQ ID NO: 42)
53 L Y S S P S Y F E N L 1322.2 (SEQ ID NO: 43)	(SEQ ID NO: 43)
54 L Y S S P S Y Y E N L 1338.2 (SEQ ID NO: 44)	(SEQ ID NO: 44)
55 L Y S S P S Y W E N L 1361.3 (SEQ ID NO: 45)	(SEQ ID NO: 45)
57 L Y S S P S D P E N L 1224.1 (SEQ ID NO: 46)	(SEQ ID NO: 58)
58 L Y S S P S D F E N L 1274.1 (SEQ ID NO: 47)	(SEQ ID NO: 61)
59 L Y S S P S D Y E N L 1290.1 (SEQ ID NO: 48)	(SEQ ID NO: 74)
60 L Y S S P S D W E N L 1313.2 (SEQ ID NO: 49)	(SEQ ID NO: 75)
62 L Y S S P S E P E N L 1238.1	[redacted]
	95 L Y T S P S Y W E N L 1374.5 (SEQ ID NO: 77)
64 L Y S S P S E Y E N L 1304.1	117 L Y T S P S H P E N L 1259.4

(SEQ ID NO: 52)

65 L Y S S P S E W E N L 1327.2

(SEQ ID NO: 53)

67 L Y S S P S N P E N L 1223.2

(SEQ ID NO: 54)

68 L Y S S P S N F E N L 1273.2

(SEQ ID NO: 55)

69 L Y S S P S N Y E N L 1289.2

(SEQ ID NO: 56)

70 L Y S S P S N W E N L 1312.3

(SEQ ID NO: 57)

72 L Y S S P S Q P E N L 1237.2

(SEQ ID NO: 58)

73 L Y S S P S Q F E N L 1287.2

(SEQ ID NO: 59)

74 L Y S S P S Q Y E N L 1303.2

(SEQ ID NO: 60)

75 L Y S S P S Q W E N L 1326.3

(SEQ ID NO: 61)

77 L Y S S P S H P E N L 1246.2

(SEQ ID NO: 62)

78 L Y S S P S H F E N L 1296.2

(SEQ ID NO: 63)

79 L Y S S P S H Y E N L 1312.2

(SEQ ID NO: 64)

80 L Y S S P S H W E N L 1335.3

(SEQ ID NO: 65)

82 L Y T S P S M P E N L 1253.5

(SEQ ID NO: 66)

83 L Y T S P S M F E N L 1303.5

(SEQ ID NO: 67)

84 L Y T S P S M Y E N L 1319.5

(SEQ ID NO: 68)

85 L Y T S P S M W E N L 1342.6

(SEQ ID NO: 69)

87 L Y T S P S F P E N L 1269.4

(SEQ ID NO: 70)

(SEQ ID NO: 94)

118 L Y T S P S H F E N L 1309.4

(SEQ ID NO: 95)

119 L Y T S P S H Y E N L 1325.4

(SEQ ID NO: 96)

120 L Y T S P S H W E N L 1348.5

(SEQ ID NO: 97)

132 L Y H S P S Y P E N L 1321.5

(SEQ ID NO: 106)

133 L Y H S P S Y F E N L 1371.5

(SEQ ID NO: 107)

[redacted]

135 L Y H S P S Y W E N L 1410.6

(SEQ ID NO: 109)

1127 W Y R S P S F P E N L 1397.6

(SEQ ID NO: 902)

1128 W Y R S P S F F E N L 1447.6

(SEQ ID NO: 903)

1129 W Y R S P S F Y E N L 1463.6

(SEQ ID NO: 904)

1130 W Y R S P S F W E N L 1486.7

(SEQ ID NO: 905)

[redacted]

372 L F T S P S Y P E N L 1269.4

(SEQ ID NO: 298)

373 L F T S P S Y F E N L 1319.4

(SEQ ID NO: 299)

[redacted]

88 L Y T S P S F F E N L	1319.4
(SEQ ID NO: 71)	
89 L Y T S P S F Y E N L	1335.4
(SEQ ID NO: 72)	
90 L Y T S P S F W E N L	1358.5
(SEQ ID NO: 73)	
92 L Y T S P S Y P E N L	1285.4
(SEQ ID NO: 74)	
93 L Y T S P S Y F E N L	1335.4
(SEQ ID NO: 75)	
[redacted]	
95 L Y T S P S Y W E N L	1374.5
(SEQ ID NO: 77)	
97 L Y T S P S D P E N L	1237.3
(SEQ ID NO: 78)	
98 L Y T S P S D F E N L	1287.3
(SEQ ID NO: 79)	
99 L Y T S P S D Y E N L	1303.3
(SEQ ID NO: 80)	
100 L Y T S P S D W E N L	1326.4
(SEQ ID NO: 81)	
102 L Y T S P S E P E N L	1251.3
(SEQ ID NO: 82)	
103 L Y T S P S E F E N L	1301.3
(SEQ ID NO: 83)	
104 L Y T S P S E Y E N L	1317.3
(SEQ ID NO: 84)	
105 L Y T S P S E W E N L	1340.4
(SEQ ID NO: 85)	
107 L Y T S P S N P E N L	1236.4
(SEQ ID NO: 86)	
108 L Y T S P S N F E N L	1286.4
(SEQ ID NO: 87)	
109 L Y T S P S N Y E N L	1302.4
(SEQ ID NO: 88)	
110 L Y T S P S N W E N L	1325.5

375 L F T S P S Y W E N L	1358.5
(SEQ ID NO: 301)	
637 F Y S S P S H P E N L	1280.2
(SEQ ID NO: 510)	
638 F Y S S P S H F E N L	1330.2
(SEQ ID NO: 511)	
639 F Y S S P S H Y E N L	1346.2
(SEQ ID NO: 512)	
640 F Y S S P S H W E N L	1369.3
(SEQ ID NO: 513)	
642 F Y T S P S M P E N L	1287.5
(SEQ ID NO: 514)	
643 F Y T S P S M F E N L	1337.5
(SEQ ID NO: 515)	
644 F Y T S P S M Y E N L	1353.5
(SEQ ID NO: 516)	
645 F Y T S P S M W E N L	1376.6
(SEQ ID NO: 517)	
647 F Y T S P S F P E N L	1303.4
(SEQ ID NO: 518)	
648 F Y T S P S F F E N L	1353.4
(SEQ ID NO: 519)	
649 F Y T S P S F Y E N L	1369.4
(SEQ ID NO: 520)	
650 F Y T S P S F W E N L	1392.5
(SEQ ID NO: 521)	
652 F Y T S P S Y P E N L	1319.4
(SEQ ID NO: 522)	
653 F Y T S P S Y F E N L	1369.4
(SEQ ID NO: 523)	
654 F Y T S P S Y Y E N L	1385.4
(SEQ ID NO: 524)	
655 F Y T S P S Y W E N L	1408.5
(SEQ ID NO: 525)	
1202 W Y T S P S M P E N L	1326.6
(SEQ ID NO: 962)	
1203 W Y T S P S M F E N L	1376.6

(SEQ ID NO: 89)

112 L Y T S P S Q P E N L 1250.4
(SEQ ID NO: 90)

113 L Y T S P S Q F E N L 1300.4
(SEQ ID NO: 91)

114 L Y T S P S Q Y E N L 1316.4
(SEQ ID NO: 92)

115 L Y T S P S Q W E N L 1339.5
(SEQ ID NO: 93)

117 L Y T S P S H P E N L 1259.4
(SEQ ID NO: 94)

118 L Y T S P S H F E N L 1309.4
(SEQ ID NO: 95)

119 L Y T S P S H Y E N L 1325.4
(SEQ ID NO: 96)

120 L Y T S P S H W E N L 1348.5
(SEQ ID NO: 97)

122 L Y H S P S M P E N L 1289.6
(SEQ ID NO: 98)

123 L Y H S P S M F E N L 1339.6
(SEQ ID NO: 99)

124 L Y H S P S M Y E N L 1355.6
(SEQ ID NO: 100)

125 L Y H S P S M W E N L 1378.7
(SEQ ID NO: 101)

127 L Y H S P S F P E N L 1305.5
(SEQ ID NO: 102)

128 L Y H S P S F F E N L 1355.5
(SEQ ID NO: 103)

129 L Y H S P S F Y E N L 1371.5
(SEQ ID NO: 104)

130 L Y H S P S F W E N L 1394.6

[illegible]
(SEQ ID NO: 106)

133 L Y H S P S Y F E N L 1371.5
(SEQ ID NO: 107)

(SEQ ID NO: 963)

1204 W Y T S P S M Y E N L 1392.6
(SEQ ID NO: 964)

1205 W Y T S P S M W E N L 1415.7
(SEQ ID NO: 965)

1207 W Y T S P S F P E N L 1342.5
(SEQ ID NO: 966)

1208 W Y T S P S F F E N L 1392.5
(SEQ ID NO: 967)

1209 W Y T S P S F Y E N L 1408.5
(SEQ ID NO: 968)

1210 W Y T S P S F W E N L 1431.6
(SEQ ID NO: 969)

1212 W Y T S P S Y P E N L 1358.5
(SEQ ID NO: 970)

1213 W Y T S P S Y F E N L 1408.5
(SEQ ID NO: 971)

1214 W Y T S P S Y Y E N L 1424.5
(SEQ ID NO: 972)

1215 W Y T S P S Y W E N L 1447.6
(SEQ ID NO: 973)

1 R Y S L P P E L S N M 1308.6
(SEQ ID NO: 1)

2 L Y R S P S M P E N L 1308.6
(SEQ ID NO: 2)

2274 L K R S P S M P E N L 1273.6
(SEQ ID NO: 1826)

2342 L Y R S P S M V E N L 1310.6
(SEQ ID NO: 1894)

2292 L Y I S P S M P E N L 1265.6
(SEQ ID NO: 1844)

2254 K Y R S P S M P E N L 1323.6
(SEQ ID NO: 1806)

135 L Y H S P S Y W E N L 1410.6	-	(SEQ ID NO: 108)
137 L Y H S P S D P E N L 1273.4	-	(SEQ ID NO: 109)
138 L Y H S P S D F E N L 1323.4	-	(SEQ ID NO: 110)
139 L Y H S P S D Y E N L 1339.4	-	(SEQ ID NO: 111)
140 L Y H S P S D W E N L 1362.5	-	(SEQ ID NO: 112)
142 L Y H S P S E P E N L 1287.4	-	(SEQ ID NO: 113)
143 L Y H S P S E F E N L 1337.4	-	(SEQ ID NO: 114)
144 L Y H S P S E Y E N L 1353.4	-	(SEQ ID NO: 115)
145 L Y H S P S E W E N L 1376.5	-	(SEQ ID NO: 116)
147 L Y H S P S N P E N L 1272.5	-	(SEQ ID NO: 117)
148 L Y H S P S N F E N L 1322.5	-	(SEQ ID NO: 118)
149 L Y H S P S N Y E N L 1338.5	-	(SEQ ID NO: 119)
150 L Y H S P S N W E N L 1361.6	-	(SEQ ID NO: 120)
152 L Y H S P S Q P E N L 1286.5	-	(SEQ ID NO: 121)
153 L Y H S P S Q F E N L 1336.5	-	(SEQ ID NO: 122)
154 L Y H S P S Q Y E N L 1352.5	-	(SEQ ID NO: 123)
155 L Y H S P S Q W E N L 1375.6	-	(SEQ ID NO: 124)
157 L Y H S P S H P E N L 1295.5	-	(SEQ ID NO: 125)
158 L Y H S P S H F E N L 1345.5	-	(SEQ ID NO: 126)
159 L Y H S P S H Y E N L 1361.5	-	(SEQ ID NO: 127)
160 L Y H S P S H W E N L 1384.6	-	(SEQ ID NO: 128)
162 L Y N S P S M P E N L 1266.6	-	(SEQ ID NO: 129)
163 L Y N S P S M F E N L 1316.6	-	(SEQ ID NO: 130)
164 L Y N S P S M Y E N L 1332.6	-	(SEQ ID NO: 131)
165 L Y N S P S M W E N L 1355.7	-	(SEQ ID NO: 132)
167 L Y N S P S F P E N L 1282.5	-	(SEQ ID NO: 133)
168 L Y N S P S F F E N L 1332.5	-	(SEQ ID NO: 134)
169 L Y N S P S F Y E N L 1348.5	-	(SEQ ID NO: 135)
170 L Y N S P S F W E N L 1371.6	-	(SEQ ID NO: 136)
172 L Y N S P S Y P E N L 1298.5	-	(SEQ ID NO: 137)
173 L Y N S P S Y F E N L 1348.5	-	(SEQ ID NO: 138)
174 L Y N S P S Y Y E N L 1364.5	-	(SEQ ID NO: 139)
		(SEQ ID NO: 140)

179 L Y N S P S D Y E N L 1316.4 (SEQ ID NO: 144)

180 L Y N S P S D W E N L 1339.5	-	(SEQ ID NO: 145)
182 L Y N S P S E P E N L 1264.4	-	(SEQ ID NO: 146)
183 L Y N S P S E F E N L 1314.4	-	(SEQ ID NO: 147)
184 L Y N S P S E Y E N L 1330.4	-	(SEQ ID NO: 148)
185 L Y N S P S E W E N L 1353.5	-	(SEQ ID NO: 149)
187 L Y N S P S N P E N L 1249.5	-	(SEQ ID NO: 150)
188 L Y N S P S N F E N L 1299.5	-	(SEQ ID NO: 151)
189 L Y N S P S N Y E N L 1315.5	-	(SEQ ID NO: 152)
190 L Y N S P S N W E N L 1338.6	-	(SEQ ID NO: 153)
192 L Y N S P S Q P E N L 1263.5	-	(SEQ ID NO: 154)
193 L Y N S P S Q F E N L 1313.5	-	(SEQ ID NO: 155)
194 L Y N S P S Q Y E N L 1329.5	-	(SEQ ID NO: 156)
195 L Y N S P S Q W E N L 1352.6	-	(SEQ ID NO: 157)
197 L Y N S P S H P E N L 1272.5	-	(SEQ ID NO: 158)
198 L Y N S P S H F E N L 1322.5	-	(SEQ ID NO: 159)
199 L Y N S P S H Y E N L 1338.5	-	(SEQ ID NO: 160)
200 L Y N S P S H W E N L 1361.6	-	(SEQ ID NO: 161)
202 L Y G S P S M P E N L 1209.5	-	(SEQ ID NO: 162)
203 L Y G S P S M F E N L 1259.5	-	(SEQ ID NO: 163)
204 L Y G S P S M Y E N L 1275.5	-	(SEQ ID NO: 164)
205 L Y G S P S M W E N L 1298.6	-	(SEQ ID NO: 165)
207 L Y G S P S F P E N L 1225.4	-	(SEQ ID NO: 166)
208 L Y G S P S F F E N L 1275.4	-	(SEQ ID NO: 167)
209 L Y G S P S F Y E N L 1291.4	-	(SEQ ID NO: 168)
210 L Y G S P S F W E N L 1314.5		(SEQ ID NO: 169)
212 L Y G S P S Y P E N L 1241.4	-	(SEQ ID NO: 170)
213 L Y G S P S Y F E N L 1291.4	-	(SEQ ID NO: 171)
214 L Y G S P S Y Y E N L 1307.4	-	(SEQ ID NO: 172)
215 L Y G S P S Y W E N L 1330.5	-	(SEQ ID NO: 173)
217 L Y G S P S D P E N L 1193.3	-	(SEQ ID NO: 174)
218 L Y G S P S D F E N L 1243.3	-	(SEQ ID NO: 175)
219 L Y G S P S D Y E N L 1259.3	-	(SEQ ID NO: 176)
220 L Y G S P S D W E N L 1282.4	-	(SEQ ID NO: 177)
[illegible]		[illegible]
[illegible]		[illegible]
225 L Y G S P S E W E N L 1296.4		(SEQ ID NO: 181)

227	L Y G S P S N P E N L	1192.4	- (SEQ ID NO: 182)
228	L Y G S P S N F E N L	1242.4	- (SEQ ID NO: 183)
229	L Y G S P S N Y E N L	1258.4	- (SEQ ID NO: 184)
230	L Y G S P S N W E N L	1281.5	- (SEQ ID NO: 185)
232	L Y G S P S Q P E N L	1206.4	- (SEQ ID NO: 186)
233	L Y G S P S Q F E N L	1256.4	- (SEQ ID NO: 187)
234	L Y G S P S Q Y E N L	1272.4	- (SEQ ID NO: 188)
235	L Y G S P S Q W E N L	1295.5	- (SEQ ID NO: 189)
237	L Y G S P S H P E N L	1215.4	- (SEQ ID NO: 190)
238	L Y G S P S H F E N L	1265.4	- (SEQ ID NO: 191)
239	L Y G S P S H Y E N L	1281.4	- (SEQ ID NO: 192)
240	L Y G S P S H W E N L	1304.5	- (SEQ ID NO: 193)
242	L Y A S P S M P E N L	1223.5	- (SEQ ID NO: 194)
243	L Y A S P S M F E N L	1273.5	- (SEQ ID NO: 195)
244	L Y A S P S M Y E N L	1289.5	- (SEQ ID NO: 196)
245	L Y A S P S M W E N L	1312.6	- (SEQ ID NO: 197)
247	L Y A S P S F P E N L	1239.4	- (SEQ ID NO: 198)
248	L Y A S P S F F E N L	1289.4	- (SEQ ID NO: 199)
249	L Y A S P S F Y E N L	1305.4	- (SEQ ID NO: 200)
250	L Y A S P S F W E N L	1328.5	- (SEQ ID NO: 201)
252	L Y A S P S Y P E N L	1255.4	- (SEQ ID NO: 202)
253	L Y A S P S Y F E N L	1305.4	- (SEQ ID NO: 203)
254	L Y A S P S Y Y E N L	1321.4	- (SEQ ID NO: 204)
255	L Y A S P S Y W E N L	1344.5	- (SEQ ID NO: 205)
257	L Y A S P S D P E N L	1207.3	- (SEQ ID NO: 206)
258	L Y A S P S D F E N L	1257.3	- (SEQ ID NO: 207)
259	L Y A S P S D Y E N L	1273.3	- (SEQ ID NO: 208)
260	L Y A S P S D W E N L	1296.4	- (SEQ ID NO: 209)
262	L Y A S P S E P E N L	1221.3	- (SEQ ID NO: 210)
263	L Y A S P S E F E N L	1271.3	- (SEQ ID NO: 211)
264	L Y A S P S E Y E N L	1287.3	- (SEQ ID NO: 212)
265	L Y A S P S E W E N L	1310.4	- (SEQ ID NO: 213)
267	L Y A S P S N P E N L	1206.4	- (SEQ ID NO: 214)
[illegible]			
272	L Y A S P S Q P E N L	1220.4	(SEQ ID NO: 218)

273 L Y A S P S Q F E N L 1270.4 - (SEQ ID NO: 219)

274 L Y A S P S Q Y E N L 1286.4 - (SEQ ID NO: 220)

275 L Y A S P S Q W E N L 1309.5 - (SEQ ID NO: 221)

277 L Y A S P S H P E N L 1229.4 - (SEQ ID NO: 222)

278 L Y A S P S H F E N L 1279.4 - (SEQ ID NO: 223)

279 L Y A S P S H Y E N L 1295.4 - (SEQ ID NO: 224)

280 L Y A S P S H W E N L 1318.5 - (SEQ ID NO: 225)

282 L F R S P S M P E N L 1292.6 - (SEQ ID NO: 226)

283 L F R S P S M F E N L 1342.6 - (SEQ ID NO: 227)

284 L F R S P S M Y E N L 1358.6 - (SEQ ID NO: 228)

285 L F R S P S M W E N L 1381.7 - (SEQ ID NO: 229)

287 L F R S P S F P E N L 1308.5 - (SEQ ID NO: 230)

288 L F R S P S F F E N L 1358.5 - (SEQ ID NO: 231)

289 L F R S P S F Y E N L 1374 5 - (SEQ ID NO: 232)

290 L F R S P S F W E N L 1397.6 - (SEQ ID NO: 233

292 L F R S P S Y P E N L 1324 5 - (SEQ ID NO: 234)

293 L F R S P S Y F E N L 1374 5 - (SEQ ID NO: 235)

294 L F R S P S Y Y E N L 1390.5 - (SEQ ID NO: 236)

295 L F R S P S Y W E N L 1413.6 - (SEQ ID NO: 237)

297 L F R S P S D P E N L 1276 4 - (SEQ ID NO: 238)

298 L F R S P S D F E N L 1326.4 - (SEQ ID NO: 239)

299 L F R S P S D Y E N L 1342.4 - (SEQ ID NO: 240)

300 L F R S P S D W E N L 1365.5 - (SEQ ID NO: 241)

302 L F R S P S E P E N L 1290.4 - (SEQ ID NO: 242)

303 L F R S P S E F E N L 1340.4 - (SEQ ID NO: 243)

304 L F R S P S E Y E N L 1356.4 - (SEQ ID NO: 244)

305 L F R S P S E W E N L 1379.5 - (SEQ ID NO: 245)

307 L F R S P S N P E N L 1275.5 - (SEQ ID NO: 246)

308 L F R S P S N F E N L 1325.5 - (SEQ ID NO: 247)

309 L F R S P S N Y E N L 1341.5 - (SEQ ID NO: 248)

310 L F R S P S N W E N L 1364.6 - (SEQ ID NO: 249)

312 L F R S P S Q P E N L 1289.5 - (SEQ ID NO: 250)

313 L F R S P S Q F E N L 1339.5 - (SEQ ID NO: 251)

[illegible]

318 L F R S P S H F E N L 1348.5 (SEQ ID NO: 255)

319 L F R S P S H Y E N L 1364.5	-	(SEQ ID NO: 256)
320 L F R S P S H W E N L 1387.6	-	(SEQ ID NO: 257)
322 L F S S P S M P E N L 1224.3	-	(SEQ ID NO: 258)
323 L F S S P S M F E N L 1274.3	-	(SEQ ID NO: 259)
324 L F S S P S M Y E N L 1290.3	-	(SEQ ID NO: 260)
325 L F S S P S M W E N L 1313.4	-	(SEQ ID NO: 261)
327 L F S S P S F P E N L 1240.2	-	(SEQ ID NO: 262)
328 L F S S P S F F E N L 1290.2	-	(SEQ ID NO: 263)
329 L F S S P S F Y E N L 1306.2	-	(SEQ ID NO: 264)
330 L F S S P S F W E N L 1329.3	-	(SEQ ID NO: 265)
332 L F S S P S Y P E N L 1256.2	-	(SEQ ID NO: 266)
333 L F S S P S Y F E N L 1306.2	-	(SEQ ID NO: 267)
334 L F S S P S Y Y E N L 1322.2	-	(SEQ ID NO: 268)
335 L F S S P S Y W E N L 1345.3	-	(SEQ ID NO: 269)
337 L F S S P S D P E N L 1208.1	-	(SEQ ID NO: 270)
338 L F S S P S D F E N L 1258.1	-	(SEQ ID NO: 271)
339 L F S S P S D Y E N L 1274.1	-	(SEQ ID NO: 272)
340 L F S S P S D W E N L 1297.2	-	(SEQ ID NO: 273)
342 L F S S P S E P E N L 1222.1	-	(SEQ ID NO: 274)
343 L F S S P S E F E N L 1272.1	-	(SEQ ID NO: 275)
344 L F S S P S E Y E N L 1288.1	-	(SEQ ID NO: 276)
345 L F S S P S E W E N L 1311.2	-	(SEQ ID NO: 277)
347 L F S S P S N P E N L 1207.2	-	(SEQ ID NO: 278)
348 L F S S P S N F E N L 1257.2	-	(SEQ ID NO: 279)
349 L F S S P S N Y E N L 1273.2	-	(SEQ ID NO: 280)
350 L F S S P S N W E N L 1296.3	-	(SEQ ID NO: 281)
352 L F S S P S Q P E N L 1221.2	-	(SEQ ID NO: 282)
353 L F S S P S Q F E N L 1271.2	-	(SEQ ID NO: 283)
354 L F S S P S Q Y E N L 1287.2	-	(SEQ ID NO: 284)
355 L F S S P S Q W E N L 1310.3	-	(SEQ ID NO: 285)
357 L F S S P S H P E N L 1230.2	-	(SEQ ID NO: 286)
358 L F S S P S H F E N L 1280.2	-	(SEQ ID NO: 287)
359 L F S S P S H Y E N L 1296.2	-	(SEQ ID NO: 288)
[illegible]	[illegible]	[illegible]

364 L F I S P S M Y E N L [illegible]	[illegible]	(SEQ ID NO: 292)

365	L F T S P S M W E N L	1326.6	-	(SEQ ID NO: 293)
367	L F T S P S F P E N L	1253.4	-	(SEQ ID NO: 294)
368	L F T S P S F F E N L	1303.4	-	(SEQ ID NO: 295)
369	L F T S P S F Y E N L	1319.4	-	(SEQ ID NO: 296)
370	L F T S P S F W E N L	1342.5	-	(SEQ ID NO: 297)
372	**L F T S P S Y P E N L**	**1269.4**	-	(SEQ ID NO: 298)
373	**L F T S P S Y F E N L**	**1319.4**	-	(SEQ ID NO: 299)
[redacted]			- - -	(SEQ ID NO: 300)
375	**L F T S P S Y W E N L**	**1358.5**	-	(SEQ ID NO: 301)
377	L F T S P S D P E N L	1221.3	-	(SEQ ID NO: 302)
378	L F T S P S D F E N L	1271.3	-	(SEQ ID NO: 303)
379	L F T S P S D Y E N L	1287.3	-	(SEQ ID NO: 304)
380	L F T S P S D W E N L	1310.4	-	(SEQ ID NO: 305)
382	L F T S P S E P E N L	1235.3	-	(SEQ ID NO: 306)
383	L F T S P S E F E N L	1285.3	-	(SEQ ID NO: 307)
384	L F T S P S E Y E N L	1301.3	-	(SEQ ID NO: 308)
385	L F T S P S E W E N L	1324.4	-	(SEQ ID NO: 309)
387	L F T S P S N P E N L	1220.4	-	(SEQ ID NO: 310)
388	L F T S P S N F E N L	1270.4	-	(SEQ ID NO: 311)
389	L F T S P S N Y E N L	1286.4	-	(SEQ ID NO: 312)
390	L F T S P S N W E N L	1309.5	-	(SEQ ID NO: 313)
392	L F T S P S Q P E N L	1234.4	-	(SEQ ID NO: 314)
393	L F T S P S Q F E N L	1284.4	-	(SEQ ID NO: 315)
394	L F T S P S Q Y E N L	1300.4	-	(SEQ ID NO: 316)
395	L F T S P S Q W E N L	1323.5	-	(SEQ ID NO: 317)
397	L F T S P S H P E N L	1243.4	-	(SEQ ID NO: 318)
398	L F T S P S H F E N L	1293.4	-	(SEQ ID NO: 319)
399	L F T S P S H Y E N L	1309.4	-	(SEQ ID NO: 320)
400	L F T S P S H W E N L	1332.5	-	(SEQ ID NO: 321)
402	L F H S P S M P E N L	1273.6	-	(SEQ ID NO: 322)
403	L F H S P S M F E N L	1323.6	-	(SEQ ID NO: 323)
404	L F H S P S M Y E N L	1339.6	-	(SEQ ID NO: 324)
405	L F H S P S M W E N L	1362.7	-	(SEQ ID NO: 325)
407	L F H S P S I P E N L	1260.5	-	(SEQ ID NO: 326)
410	L F H S P S I W E N L	1379.6	-	(SEQ ID NO: 329)

412 L F H S P S Y P E N L 1305.5 - (SEQ ID NO: 330)

413 L F H S P S Y F E N L 1355.5 - (SEQ ID NO: 331)

414 L F H S P S Y Y E N L 1371.5 - (SEQ ID NO: 332)

415 L F H S P S Y W E N L 1394.6 - (SEQ ID NO: 333)

417 L F H S P S D P E N L 1257.4 - (SEQ ID NO: 334)

418 L F H S P S D F E N L 1307.4 - (SEQ ID NO: 335)

419 L F H S P S D Y E N L 1323.4 - (SEQ ID NO: 336)

420 L F H S P S D W E N L 1346.5 - (SEQ ID NO: 337)

422 L F H S P S E P E N L 1271.4 - (SEQ ID NO: 338)

423 L F H S P S E F E N L 1321.4 - (SEQ ID NO: 339)

424 L F H S P S E Y E N L 1337.4 - (SEQ ID NO: 340)

425 L F H S P S E W E N L 1360.5 - (SEQ ID NO: 341)

427 L F H S P S N P E N L 1256.5 - (SEQ ID NO: 342)

428 L F H S P S N F E N L 1306.5 - (SEQ ID NO: 343)

429 L F H S P S N Y E N L 1322.5 - (SEQ ID NO: 344)

430 L F H S P S N W E N L 1345.6 - (SEQ ID NO: 345)

432 L F H S P S Q P E N L 1270.5 - (SEQ ID NO: 346)

433 L F H S P S Q F E N L 1320.5 - (SEQ ID NO: 347)

434 L F H S P S Q Y E N L 1336.5 - (SEQ ID NO: 348)

435 L F H S P S Q W E N L 1359.6 - (SEQ ID NO: 349)

437 L F H S P S H P E N L 1279.5 - (SEQ ID NO: 350)

438 L F H S P S H F E N L 1329.5 - (SEQ ID NO: 351)

439 L F H S P S H Y E N L 1345.5 - (SEQ ID NO: 352)

440 L F H S P S H W E N L 1368.6 - (SEQ ID NO: 353)

442 L F N S P S M P E N L 1250.6 - (SEQ ID NO: 354)

443 L F N S P S M F E N L 1300.6 - (SEQ ID NO: 355)

444 L F N S P S M Y E N L 1316.6 - (SEQ ID NO: 356)

445 L F N S P S M W E N L 1339.7 - (SEQ ID NO: 357)

447 L F N S P S F P E N L 1266.5 - (SEQ ID NO: 358)

448 L F N S P S F F E N L 1316.5 - (SEQ ID NO: 359)

449 L F N S P S F Y E N L 1332.5 - (SEQ ID NO: 360)

450 L F N S P S F W E N L 1355.6 - (SEQ ID NO: 361)

452 L F N S P S Y P E N L 1282.5 - (SEQ ID NO: 362)

[illegible]

[illegible] L F N S P S D P E N L 1254.4 (SEQ ID NO: 366)

458 L F N S P S D F E N L 1284.4	-	(SEQ ID NO: 367)
459 L F N S P S D Y E N L 1300.4	-	(SEQ ID NO: 368)
460 L F N S P S D W E N L 1323.5	-	(SEQ ID NO: 369)
462 L F N S P S E P E N L 1248.4	-	(SEQ ID NO: 370)
463 L F N S P S E F E N L 1298.4	-	(SEQ ID NO: 371)
464 L F N S P S E Y E N L 1314.4	-	(SEQ ID NO: 372)
465 L F N S P S E W E N L 1337.5	-	(SEQ ID NO: 373)
467 L F N S P S N P E N L 1233.5	-	(SEQ ID NO: 374)
468 L F N S P S N F E N L 1283.5	-	(SEQ ID NO: 375)
469 L F N S P S N Y E N L 1299.5	-	(SEQ ID NO: 376)
470 L F N S P S N W E N L 1322.6	-	(SEQ ID NO: 377)
472 L F N S P S Q P E N L 1247.5	-	(SEQ ID NO: 378)
473 L F N S P S Q F E N L 1297.5	-	(SEQ ID NO: 379)
474 L F N S P S Q Y E N L 1313.5	-	(SEQ ID NO: 380)
475 L F N S P S Q W E N L 1336.6	-	(SEQ ID NO: 381)
477 L F N S P S H P E N L 1256.5	-	(SEQ ID NO: 382)
478 L F N S P S H F E N L 1306.5	-	(SEQ ID NO: 383)
479 L F N S P S H Y E N L 1322.5	-	(SEQ ID NO: 384)
480 L F N S P S H W E N L 1345.6	-	(SEQ ID NO: 385)
482 L F G S P S M P E N L 1193.5	-	(SEQ ID NO: 386)
483 L F G S P S M F E N L 1243.5	-	(SEQ ID NO: 387)
484 L F G S P S M Y E N L 1259.5	-	(SEQ ID NO: 388)
485 L F G S P S M W E N L 1282.6	-	(SEQ ID NO: 389)
487 L F G S P S F P E N L 1209.4	-	(SEQ ID NO: 390)
488 L F G S P S F F E N L 1259.4	-	(SEQ ID NO: 391)
489 L F G S P S F Y E N L 1275.4	-	(SEQ ID NO: 392)
490 L F G S P S F W E N L 1298.5	-	(SEQ ID NO: 393)
492 L F G S P S Y P E N L 1225.4	-	(SEQ ID NO: 394)
493 L F G S P S Y F E N L 1275.4	-	(SEQ ID NO: 395)
494 L F G S P S Y Y E N L 1291.4	-	(SEQ ID NO: 396)
495 L F G S P S Y W E N L 1314.5	-	(SEQ ID NO: 397)
497 L F G S P S D P E N L 1177.3	-	(SEQ ID NO: 398)
498 L F G S P S D F E N L 1227.3	-	(SEQ ID NO: 399)
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
503 L F G S P S I F E N L 1241.5	-	(SEQ ID NO: 400)

504 L F G S P S E Y E N L 1257.3	-	(SEQ ID NO: 404)
505 L F G S P S E W E N L 1280.4	-	(SEQ ID NO: 405)
507 L F G S P S N P E N L 1176.4	-	(SEQ ID NO: 406)
508 L F G S P S N F E N L 1226.4	-	(SEQ ID NO: 407)
509 L F G S P S N Y E N L 1242.4	-	(SEQ ID NO: 408)
510 L F G S P S N W E N L 1265.5	-	(SEQ ID NO: 409)
512 L F G S P S Q P E N L 1190.4	-	(SEQ ID NO: 410)
513 L F G S P S Q F E N L 1240.4	-	(SEQ ID NO: 411)
514 L F G S P S Q Y E N L 1256.4	-	(SEQ ID NO: 412)
515 L F G S P S Q W E N L 1279.5	-	(SEQ ID NO: 413)
517 L F G S P S H P E N L 1199.4	-	(SEQ ID NO: 414)
518 L F G S P S H F E N L 1249.4	-	(SEQ ID NO: 415)
519 L F G S P S H Y E N L 1265.4	-	(SEQ ID NO: 416)
520 L F G S P S H W E N L 1288.5	-	(SEQ ID NO: 417)
522 L F A S P S M P E N L 1207.5	-	(SEQ ID NO: 418)
523 L F A S P S M F E N L 1257.5	-	(SEQ ID NO: 419)
524 L F A S P S M Y E N L 1273.5	-	(SEQ ID NO: 420)
525 L F A S P S M W E N L 1296.6	-	(SEQ ID NO: 421)
527 L F A S P S F P E N L 1223.4	-	(SEQ ID NO: 422)
528 L F A S P S F F E N L 1273.4	-	(SEQ ID NO: 423)
529 L F A S P S F Y E N L 1289.4	-	(SEQ ID NO: 424)
530 L F A S P S F W E N L 1312.5	-	(SEQ ID NO: 425)
532 L F A S P S Y P E N L 1239.4	-	(SEQ ID NO: 426)
533 L F A S P S Y F E N L 1289.4	-	(SEQ ID NO: 427)
534 L F A S P S Y Y E N L 1305.4	-	(SEQ ID NO: 428)
535 L F A S P S Y W E N L 1328.5	-	(SEQ ID NO: 429)
537 L F A S P S D P E N L 1191.3	-	(SEQ ID NO: 430)
538 L F A S P S D F E N L 1241.3	-	(SEQ ID NO: 431)
539 L F A S P S D Y E N L 1257.3	-	(SEQ ID NO: 432)
540 L F A S P S D W E N L 1280.4	-	(SEQ ID NO: 433)
542 L F A S P S E P E N L 1205.3	-	(SEQ ID NO: 434)
543 L F A S P S E F E N L 1255.3	-	(SEQ ID NO: 435)
544 L F A S P S E Y E N L 1271.3	-	(SEQ ID NO: 436)

549 L F A S P S N Y E N L 1256.4 (SEQ ID NO: 440)

550 L F A S P S N W E N L 1279.5 - (SEQ ID NO: 441)

552 L F A S P S Q P E N L 1204.4 - (SEQ ID NO: 442)

553 L F A S P S Q F E N L 1254.4 - (SEQ ID NO: 443)

554 L F A S P S Q Y E N L 1270.4 - (SEQ ID NO: 444)

555 L F A S P S Q W E N L 1293.5 - (SEQ ID NO: 445)

557 L F A S P S H P E N L 1213.4 - (SEQ ID NO: 446)

558 L F A S P S H F E N L 1263.4 - (SEQ ID NO: 447)

559 L F A S P S H Y E N L 1279.4 - (SEQ ID NO: 448)

560 L F A S P S H W E N L 1302.5 - (SEQ ID NO: 449)

562 F Y R S P S M P E N L 1342.6 - (SEQ ID NO: 450)

563 F Y R S P S M F E N L 1392.6 - (SEQ ID NO: 451)

564 F Y R S P S M Y E N L 1408.6 - (SEQ ID NO: 452)

565 F Y R S P S M W E N L 1431.7 - (SEQ ID NO: 453)

567 F Y R S P S F P E N L 1358.5 - (SEQ ID NO: 454)

568 F Y R S P S F F E N L 1408.5 - (SEQ ID NO: 455)

569 F Y R S P S F Y E N L 1424.5 - (SEQ ID NO: 456)

570 F Y R S P S F W E N L 1447.6 - (SEQ ID NO: 457)

572 F Y R S P S Y P E N L 1374.5 - (SEQ ID NO: 458)

573 F Y R S P S Y F E N L 1424.5 - (SEQ ID NO: 459)

574 F Y R S P S Y Y E N L 1440.5 - (SEQ ID NO: 460)

575 F Y R S P S Y W E N L 1463.6 - (SEQ ID NO: 461)

577 F Y R S P S D P E N L 1326.4 - (SEQ ID NO: 462)

578 F Y R S P S D F E N L 1376.4 - (SEQ ID NO: 463)

579 F Y R S P S D Y E N L 1392.4 - (SEQ ID NO: 464)

580 F Y R S P S D W E N L 1415.5 - (SEQ ID NO: 465)

582 F Y R S P S E P E N L 1340.4 - (SEQ ID NO: 466)

583 F Y R S P S E F E N L 1390.4 - (SEQ ID NO: 467)

584 F Y R S P S E Y E N L 1406.4 - (SEQ ID NO: 468)

585 F Y R S P S E W E N L 1429.5 - (SEQ ID NO: 469)

587 F Y R S P S N P E N L 1325.5 - (SEQ ID NO: 470)

588 F Y R S P S N F E N L 1375.5 - (SEQ ID NO: 471)

589 F Y R S P S N Y E N L 1391.5 - (SEQ ID NO: 472)

590 F Y R S P S N W E N L 1414.6 - (SEQ ID NO: 473)

595 F Y R S P S Q W E N L 1428.6 - (SEQ ID NO: 474)

597 F Y R S P S H P E N L 1348.5	-	(SEQ ID NO: 478)
598 F Y R S P S H F E N L 1398.5	-	(SEQ ID NO: 479)
599 F Y R S P S H Y E N L 1414.5	-	(SEQ ID NO: 480)
600 F Y R S P S H W E N L 1437.6	-	(SEQ ID NO: 481)
602 F Y S S P S M P E N L 1274.3	-	(SEQ ID NO: 482)
603 F Y S S P S M F E N L 1324.3	-	(SEQ ID NO: 483)
604 F Y S S P S M Y E N L 1340.3	-	(SEQ ID NO: 484)
605 F Y S S P S M W E N L 1363.4	-	(SEQ ID NO: 485)
607 F Y S S P S F P E N L 1290.2	-	(SEQ ID NO: 486)
608 F Y S S P S F F E N L 1340.2	-	(SEQ ID NO: 487)
609 F Y S S P S F Y E N L 1356.2	-	(SEQ ID NO: 488)
610 F Y S S P S F W E N L 1379.3	-	(SEQ ID NO: 489)
612 F Y S S P S Y P E N L 1306.2	-	(SEQ ID NO: 490)
613 F Y S S P S Y F E N L 1356.2	-	(SEQ ID NO: 491)
614 F Y S S P S Y Y E N L 1372.2	-	(SEQ ID NO: 492)
615 F Y S S P S Y W E N L 1395.3	-	(SEQ ID NO: 493)
617 F Y S S P S D P E N L 1258.1	-	(SEQ ID NO: 494)
618 F Y S S P S D F E N L 1308.1	-	(SEQ ID NO: 495)
619 F Y S S P S D Y E N L 1324.1	-	(SEQ ID NO: 496)
620 F Y S S P S D W E N L 1347.2	-	(SEQ ID NO: 497)
622 F Y S S P S E P E N L 1272.1	-	(SEQ ID NO: 498)
623 F Y S S P S E F E N L 1322.1	-	(SEQ ID NO: 499)
624 F Y S S P S E Y E N L 1338.1	-	(SEQ ID NO: 500)
625 F Y S S P S E W E N L 1361.2	-	(SEQ ID NO: 501)
627 F Y S S P S N P E N L 1257.2	-	(SEQ ID NO: 502)
628 F Y S S P S N F E N L 1307.2	-	(SEQ ID NO: 503)
629 F Y S S P S N Y E N L 1323.2	-	(SEQ ID NO: 504)
630 F Y S S P S N W E N L 1346.3	-	(SEQ ID NO: 505)
632 F Y S S P S Q P E N L 1271.2	-	(SEQ ID NO: 506)
633 F Y S S P S Q F E N L 1321.2	-	(SEQ ID NO: 507)
634 F Y S S P S Q Y E N L 1337.2	-	(SEQ ID NO: 508)
635 F Y S S P S Q W E N L 1360.3	-	(SEQ ID NO: 509)
637 F Y S S P S H P E N L 1280.2	-	(SEQ ID NO: 510)
638 F Y S S P S H F E N L 1330.2		
639 F Y S S P S H Y E N L 1346.2		
640 F Y S S P S H W E N L 1369.3		
642 F Y T S P S M P E N L 1287.5		(SEQ ID NO: 514)

643	**FYTSPSMFENL**	**1337.5**	(SEQ ID NO: 515)
644	**FYTSPSMYENL**	**1353.5**	(SEQ ID NO: 516)
645	**FYTSPSMWENL**	**1376.6**	(SEQ ID NO: 517)
647	**FYTSPSFPENL**	**1303.4**	(SEQ ID NO: 518)
648	**FYTSPSFFENL**	**1353.4**	(SEQ ID NO: 519)
649	**FYTSPSFYENL**	**1369.4**	(SEQ ID NO: 520)
650	**FYTSPSFWENL**	**1392.5**	(SEQ ID NO: 521)
652	**FYTSPSYPENL**	**1319.4**	(SEQ ID NO: 522)
653	**FYTSPSYFENL**	**1369.4**	(SEQ ID NO: 523)
654	**FYTSPSYYENL**	**1385.4**	(SEQ ID NO: 524)
655	**FYTSPSYWENL**	**1408.5**	(SEQ ID NO: 525)
657	FYTSPSDPENL	1271.3	(SEQ ID NO: 526)
658	FYTSPSDFENL	1321.3	(SEQ ID NO: 527)
659	FYTSPSDYENL	1337.3	(SEQ ID NO: 528)
660	FYTSPSDWENL	1360.4	(SEQ ID NO: 529)
662	FYTSPSEPENL	1285.3	(SEQ ID NO: 530)
663	FYTSPSEFENL	1335.3	(SEQ ID NO: 531)
664	FYTSPSEYENL	1351.3	(SEQ ID NO: 532)
665	FYTSPSEWENL	1374.4	(SEQ ID NO: 533)
667	FYTSPSNPENL	1270.4	(SEQ ID NO: 534)
668	FYTSPSNFENL	1320.4	(SEQ ID NO: 535)
669	FYTSPSNYENL	1336.4	(SEQ ID NO: 536)
670	FYTSPSNWENL	1359.5	(SEQ ID NO: 537)
672	FYTSPSQPENL	1284.4	(SEQ ID NO: 538)
673	FYTSPSQFENL	1334.4	(SEQ ID NO: 539)
674	FYTSPSQYENL	1350.4	(SEQ ID NO: 540)
675	FYTSPSQWENL	1373.5	(SEQ ID NO: 541)
677	FYTSPSHPENL	1293.4	(SEQ ID NO: 542)
678	FYTSPSHFENL	1343.4	(SEQ ID NO: 543)
679	FYTSPSHYENL	1359.4	(SEQ ID NO: 544)
680	FYTSPSHWENL	1382.5	(SEQ ID NO: 545)
682	FYHSPSMPENL	1323.6	(SEQ ID NO: 546)
683	FYHSPSMFENL	1373.6	(SEQ ID NO: 547)

688 FYHSPSLFENL 1389.5 (SEQ ID NO: 551)

689 F Y H S P S F Y E N L 1405.5	-	(SEQ ID NO: 552)
690 F Y H S P S F W E N L 1428.6	-	(SEQ ID NO: 553)
692 F Y H S P S Y P E N L 1355.5	-	(SEQ ID NO: 554)
693 F Y H S P S Y F E N L 1405.5	-	(SEQ ID NO: 555)
694 F Y H S P S Y Y E N L 1421.5	-	(SEQ ID NO: 556)
695 F Y H S P S Y W E N L 1444.6	-	(SEQ ID NO: 557)
697 F Y H S P S D P E N L 1307.4	-	(SEQ ID NO: 558)
698 F Y H S P S D F E N L 1357.4	-	(SEQ ID NO: 559)
699 F Y H S P S D Y E N L 1373.4	-	(SEQ ID NO: 560)
700 F Y H S P S D W E N L 1396.5	-	(SEQ ID NO: 561)
702 F Y H S P S E P E N L 1321.4	-	(SEQ ID NO: 562)
703 F Y H S P S E F E N L 1371.4		(SEQ ID NO: 563)
704 F Y H S P S E Y E N L 1387.4	-	(SEQ ID NO: 564)
705 F Y H S P S E W E N L 1410.5	-	(SEQ ID NO: 565)
707 F Y H S P S N P E N L 1306.5	-	(SEQ ID NO: 566)
708 F Y H S P S N F E N L 1356.5	-	(SEQ ID NO: 567)
709 F Y H S P S N Y E N L 1372.5	-	(SEQ ID NO: 568)
710 F Y H S P S N W E N L 1395.6	-	(SEQ ID NO: 569)
712 F Y H S P S Q P E N L 1320.5	-	(SEQ ID NO: 570)
713 F Y H S P S Q F E N L 1370.5	-	(SEQ ID NO: 571)
714 F Y H S P S Q Y E N L 1386.5	-	(SEQ ID NO: 572)
715 F Y H S P S Q W E N L 1409.6	-	(SEQ ID NO: 573)
717 F Y H S P S H P E N L 1329.5	-	(SEQ ID NO: 574)
718 F Y H S P S H F E N L 1379.5	-	(SEQ ID NO: 575)
719 F Y H S P S H Y E N L 1395.5	-	(SEQ ID NO: 576)
720 F Y H S P S H W E N L 1418.6	-	(SEQ ID NO: 577)
722 F Y N S P S M P E N L 1300.6	-	(SEQ ID NO: 578)
723 F Y N S P S M F E N L 1350.6	-	(SEQ ID NO: 579)
724 F Y N S P S M Y E N L 1366.6	-	(SEQ ID NO: 580)
725 F Y N S P S M W E N L 1389.7	-	(SEQ ID NO: 581)
727 F Y N S P S F P E N L 1316.5	-	(SEQ ID NO: 582)
728 F Y N S P S F F E N L 1366.5	-	(SEQ ID NO: 583)
729 F Y N S P S F Y E N L 1382.5	-	(SEQ ID NO: 584)

731 F Y N S P S Y Y E N L 1398.5	(SEQ ID NO: 585)

735 F Y N S P S Y W E N L 1421.6	-	(SEQ ID NO: 589)
737 F Y N S P S D P E N L 1284.4	-	(SEQ ID NO: 590)
738 F Y N S P S D F E N L 1334.4	-	(SEQ ID NO: 591)
739 F Y N S P S D Y E N L 1350.4	-	(SEQ ID NO: 592)
740 F Y N S P S D W E N L 1373.5	-	(SEQ ID NO: 593)
742 F Y N S P S E P E N L 1298.4	-	(SEQ ID NO: 594)
743 F Y N S P S E F E N L 1348.4	-	(SEQ ID NO: 595)
744 F Y N S P S E Y E N L 1364.4	-	(SEQ ID NO: 596)
745 F Y N S P S E W E N L 1387.5	-	(SEQ ID NO: 597)
747 F Y N S P S N P E N L 1283.5	-	(SEQ ID NO: 598)
748 F Y N S P S N F E N L 1333.5	-	(SEQ ID NO: 599)
749 F Y N S P S N Y E N L 1349.5	-	(SEQ ID NO: 600)
750 F Y N S P S N W E N L 1372.6	-	(SEQ ID NO: 601)
752 F Y N S P S Q P E N L 1297.5	-	(SEQ ID NO: 602)
753 F Y N S P S Q F E N L 1347.5	-	(SEQ ID NO: 603)
754 F Y N S P S Q Y E N L 1363.5	-	(SEQ ID NO: 604)
755 F Y N S P S Q W E N L 1386.6	-	(SEQ ID NO: 605)
757 F Y N S P S H P E N L 1306.5	-	(SEQ ID NO: 606)
758 F Y N S P S H F E N L 1356.5	-	(SEQ ID NO: 607)
759 F Y N S P S H Y E N L 1372.5	-	(SEQ ID NO: 608)
760 F Y N S P S H W E N L 1395.6	-	(SEQ ID NO: 609)
762 F Y G S P S M P E N L 1243.5	-	(SEQ ID NO: 610)
763 F Y G S P S M F E N L 1293.5	-	(SEQ ID NO: 611)
764 F Y G S P S M Y E N L 1309.5	-	(SEQ ID NO: 612)
765 F Y G S P S M W E N L 1332.6	-	(SEQ ID NO: 613)
767 F Y G S P S F P E N L 1259.4	-	(SEQ ID NO: 614)
768 F Y G S P S F F E N L 1309.4	-	(SEQ ID NO: 615)
769 F Y G S P S F Y E N L 1325.4	-	(SEQ ID NO: 616)
770 F Y G S P S F W E N L 1348.5	-	(SEQ ID NO: 617)
772 F Y G S P S Y P E N L 1275.4	-	(SEQ ID NO: 618)
773 F Y G S P S Y F E N L 1325.4	-	(SEQ ID NO: 619)
774 F Y G S P S Y Y E N L 1341.4	-	(SEQ ID NO: 620)
775 F Y G S P S Y W E N L 1364.5	-	(SEQ ID NO: 621)
[illegible]		[illegible]
780 F Y G S P S D W E N L [illegible]		(SEQ ID NO: 62[illegible])

782	F Y G S P S E P E N L	1241.3	- (SEQ ID NO: 626)
783	F Y G S P S E F E N L	1291.3	- (SEQ ID NO: 627)
784	F Y G S P S E Y E N L	1307.3	- (SEQ ID NO: 628)
785	F Y G S P S E W E N L	1330.4	- (SEQ ID NO: 629)
787	F Y G S P S N P E N L	1226.4	- (SEQ ID NO: 630)
788	F Y G S P S N F E N L	1276.4	- (SEQ ID NO: 631)
789	F Y G S P S N Y E N L	1292.4	- (SEQ ID NO: 632)
790	F Y G S P S N W E N L	1315.5	- (SEQ ID NO: 633)
792	F Y G S P S Q P E N L	1240.4	- (SEQ ID NO: 634)
793	F Y G S P S Q F E N L	1290.4	- (SEQ ID NO: 635)
794	F Y G S P S Q Y E N L	1306.4	- (SEQ ID NO: 636)
795	F Y G S P S Q W E N L	1329.5	- (SEQ ID NO: 637)
797	F Y G S P S H P E N L	1249.4	- (SEQ ID NO: 638)
798	F Y G S P S H F E N L	1299.4	- (SEQ ID NO: 639)
799	F Y G S P S H Y E N L	1315.4	- (SEQ ID NO: 640)
800	F Y G S P S H W E N L	1338.5	- (SEQ ID NO: 641)
802	F Y A S P S M P E N L	1257.5	- (SEQ ID NO: 642)
803	F Y A S P S M F E N L	1307.5	- (SEQ ID NO: 643)
804	F Y A S P S M Y E N L	1323.5	- (SEQ ID NO: 644)
805	F Y A S P S M W E N L	1346.6	- (SEQ ID NO: 645)
807	F Y A S P S F P E N L	1273.4	- (SEQ ID NO: 646)
808	F Y A S P S F F E N L	1323.4	- (SEQ ID NO: 647)
809	F Y A S P S F Y E N L	1339.4	- (SEQ ID NO: 648)
810	F Y A S P S F W E N L	1362.5	- (SEQ ID NO: 649)
812	F Y A S P S Y P E N L	1289.4	- (SEQ ID NO: 650)
813	F Y A S P S Y F E N L	1339.4	- (SEQ ID NO: 651)
814	F Y A S P S Y Y E N L	1355.4	- (SEQ ID NO: 652)
815	F Y A S P S Y W E N L	1378.5	- (SEQ ID NO: 653)
817	F Y A S P S D P E N L	1241.3	- (SEQ ID NO: 654)
818	F Y A S P S D F E N L	1291.3	- (SEQ ID NO: 655)
819	F Y A S P S D Y E N L	1307.3	- (SEQ ID NO: 656)
820	F Y A S P S D W E N L	1330.4	- (SEQ ID NO: 657)
822	F Y A S P S E P E N L	1255.3	- (SEQ ID NO: 658)

827	F Y A S P S N P E N L	1240.4	(SEQ ID NO: 662)

828 F Y A S P S N F E N L 1290.4 - (SEQ ID NO: 663)

829 F Y A S P S N Y E N L 1306.4 - (SEQ ID NO: 664)

830 F Y A S P S N W E N L 1329.5 - (SEQ ID NO: 665)

832 F Y A S P S Q P E N L 1254.4 - (SEQ ID NO: 666)

833 F Y A S P S Q F E N L 1304.4 - (SEQ ID NO: 667)

834 F Y A S P S Q Y E N L 1320.4 - (SEQ ID NO: 668)

835 F Y A S P S Q W E N L 1343.5 - (SEQ ID NO: 669)

837 F Y A S P S H P E N L 1263.4 - (SEQ ID NO: 670)

838 F Y A S P S H F E N L 1313.4 - (SEQ ID NO: 671)

839 F Y A S P S H Y E N L 1329.4 - (SEQ ID NO: 672)

840 F Y A S P S H W E N L 1352.5 - (SEQ ID NO: 673)

842 F F R S P S M P E N L 1326.6 - (SEQ ID NO: 674)

843 F F R S P S M F E N L 1376.6 - (SEQ ID NO: 675)

844 F F R S P S M Y E N L 1392.6 - (SEQ ID NO: 676)

845 F F R S P S M W E N L 1415.7 - (SEQ ID NO: 677)

847 F F R S P S F P E N L 1342.5 - (SEQ ID NO: 678)

848 F F R S P S F F E N L 1392.5 - (SEQ ID NO: 679)

849 F F R S P S F Y E N L 1408.5 - (SEQ ID NO: 680)

850 F F R S P S F W E N L 1431.6 - (SEQ ID NO: 681)

852 F F R S P S Y P E N L 1358.5 - (SEQ ID NO: 682)

853 F F R S P S Y F E N L 1408.5 - (SEQ ID NO: 683)

854 F F R S P S Y Y E N L 1424.5 - (SEQ ID NO: 684)

855 F F R S P S Y W E N L 1447.6 - (SEQ ID NO: 685)

857 F F R S P S D P E N L 1310.4 - (SEQ ID NO: 686)

858 F F R S P S D F E N L 1360.4 - (SEQ ID NO: 687)

859 F F R S P S D Y E N L 1376.4 - (SEQ ID NO: 688)

860 F F R S P S D W E N L 1399.5 - (SEQ ID NO: 689)

862 F F R S P S E P E N L 1324.4 - (SEQ ID NO: 690)

863 F F R S P S E F E N L 1374.4 - (SEQ ID NO: 691)

864 F F R S P S E Y E N L 1390.4 - (SEQ ID NO: 692)

865 F F R S P S E W E N L 1413.5 - (SEQ ID NO: 693)

867 F F R S P S N P E N L 1309.5 - (SEQ ID NO: 694)

868 F F R S P S N F E N L 1359.5 - (SEQ ID NO: 695)

[illegible] [illegible]

873 F F R S P S Q F E N L 1375.5 (SEQ ID NO: 699)

874	F F R S P S Q Y E N L	1389.5	- (SEQ ID NO: 700)
875	F F R S P S Q W E N L	1412.6	- (SEQ ID NO: 701)
877	F F R S P S H P E N L	1332.5	- (SEQ ID NO: 702)
878	F F R S P S H F E N L	1382.5	- (SEQ ID NO: 703)
879	F F R S P S H Y E N L	1398.5	- (SEQ ID NO: 704)
880	F F R S P S H W E N L	1421.6	- (SEQ ID NO: 705)
882	F F S S P S M P E N L	1258.3	- (SEQ ID NO: 706)
883	F F S S P S M F E N L	1308.3	- (SEQ ID NO: 707)
884	F F S S P S M Y E N L	1324.3	- (SEQ ID NO: 708)
885	F F S S P S M W E N L	1347.4	- (SEQ ID NO: 709)
887	F F S S P S F P E N L	1274.2	- (SEQ ID NO: 710)
888	F F S S P S F F E N L	1324.2	- (SEQ ID NO: 711)
889	F F S S P S F Y E N L	1340.2	- (SEQ ID NO: 712)
890	F F S S P S F W E N L	1363.3	- (SEQ ID NO: 713)
892	F F S S P S Y P E N L	1290.2	- (SEQ ID NO: 714)
893	F F S S P S Y F E N L	1340.2	- (SEQ ID NO: 715)
894	F F S S P S Y Y E N L	1356.2	- (SEQ ID NO: 716)
895	F F S S P S Y W E N L	1379.3	- (SEQ ID NO: 717)
897	F F S S P S D P E N L	1242.1	- (SEQ ID NO: 718)
898	F F S S P S D F E N L	1292.1	- (SEQ ID NO: 719)
899	F F S S P S D Y E N L	1308.1	- (SEQ ID NO: 720)
900	F F S S P S D W E N L	1331.2	- (SEQ ID NO: 721)
902	F F S S P S E P E N L	1256.1	- (SEQ ID NO: 722)
903	F F S S P S E F E N L	1306.1	- (SEQ ID NO: 723)
904	F F S S P S E Y E N L	1322.1	- (SEQ ID NO: 724)
905	F F S S P S E W E N L	1345.2	- (SEQ ID NO: 725)
907	F F S S P S N P E N L	1241.2	- (SEQ ID NO: 726)
908	F F S S P S N F E N L	1291.2	- (SEQ ID NO: 727)
909	F F S S P S N Y E N L	1307.2	- (SEQ ID NO: 728)
910	F F S S P S N W E N L	1330.3	- (SEQ ID NO: 729)
912	F F S S P S Q P E N L	1255.2	- (SEQ ID NO: 730)
913	F F S S P S Q F E N L	1305.2	- (SEQ ID NO: 731)
914	F F S S P S Q Y E N L	1321.2	- (SEQ ID NO: 732)
915	F F S S P S Q W E N L	1344.3	- (SEQ ID NO: 733)
919	F F S S P S H Y E N L	1380.2	- (SEQ ID NO: 736)

920 F F S S P S H W E N L 1353.3 - (SEQ ID NO: 737)

922 F F T S P S M P E N L 1271.5 - (SEQ ID NO: 738)

923 F F T S P S M F E N L 1321.5 - (SEQ ID NO: 739)

924 F F T S P S M Y E N L 1337.5 - (SEQ ID NO: 740)

925 F F T S P S M W E N L 1360.6 - (SEQ ID NO: 741)

927 F F T S P S F P E N L 1287.4 - (SEQ ID NO: 742)

928 F F T S P S F F E N L 1337.4 - (SEQ ID NO: 743)

929 F F T S P S F Y E N L 1353.4 - (SEQ ID NO: 744)

930 F F T S P S F W E N L 1376.5 - (SEQ ID NO: 745)

932 F F T S P S Y P E N L 1303.4 - (SEQ ID NO: 746)

933 F F T S P S Y F E N L 1353.4 - (SEQ ID NO: 747)

934 F F T S P S Y Y E N L 1369.4 - (SEQ ID NO: 748)

935 F F T S P S Y W E N L 1392.5 - (SEQ ID NO: 749)

937 F F T S P S D P E N L 1255.3 - (SEQ ID NO: 750)

938 F F T S P S D F E N L 1305.3 - (SEQ ID NO: 751)

939 F F T S P S D Y E N L 1321.3 - (SEQ ID NO: 752)

940 F F T S P S D W E N L 1344.4 - (SEQ ID NO: 753)

942 F F T S P S E P E N L 1269.3 - (SEQ ID NO: 754)

943 F F T S P S E F E N L 1319.3 - (SEQ ID NO: 755)

944 F F T S P S E Y E N L 1335.3 - (SEQ ID NO: 756)

945 F F T S P S E W E N L 1358.4 - (SEQ ID NO: 757)

947 F F T S P S N P E N L 1254.4 - (SEQ ID NO: 758)

948 F F T S P S N F E N L 1304.4 - (SEQ ID NO: 759)

949 F F T S P S N Y E N L 1320.4 - (SEQ ID NO: 760)

950 F F T S P S N W E N L 1343.5 - (SEQ ID NO: 761)

952 F F T S P S Q P E N L 1268.4 - (SEQ ID NO: 762)

953 F F T S P S Q F E N L 1318.4 - (SEQ ID NO: 763)

954 F F T S P S Q Y E N L 1334.4 - (SEQ ID NO: 764)

955 F F T S P S Q W E N L 1357.5 - (SEQ ID NO: 765)

957 F F T S P S H P E N L 1277.4 - (SEQ ID NO: 766)

958 F F T S P S H F E N L 1327.4 - (SEQ ID NO: 767)

959 F F T S P S H Y E N L 1343.4 - (SEQ ID NO: 768)

960 F F T S P S H W E N L 1366.5 - (SEQ ID NO: 769)

[illegible]

965 F F H S P S M W E N L 1396.[illegible] (SEQ ID NO: [illegible])

967	F F H S P S F P E N L	1323.5	- (SEQ ID NO: 774)
968	F F H S P S F F E N L	1373.5	- (SEQ ID NO: 775)
969	F F H S P S F Y E N L	1389.5	- (SEQ ID NO: 776)
970	F F H S P S F W E N L	1412.6	- (SEQ ID NO: 777)
972	F F H S P S Y P E N L	1339.5	- (SEQ ID NO: 778)
973	F F H S P S Y F E N L	1389.5	- (SEQ ID NO: 779)
974	F F H S P S Y Y E N L	1405.5	- (SEQ ID NO: 780)
975	F F H S P S Y W E N L	1428.6	- (SEQ ID NO: 781)
977	F F H S P S D P E N L	1291.4	- (SEQ ID NO: 782)
978	F F H S P S D F E N L	1341.4	- (SEQ ID NO: 783)
979	F F H S P S D Y E N L	1357.4	- (SEQ ID NO: 784)
980	F F H S P S D W E N L	1380.5	- (SEQ ID NO: 785)
982	F F H S P S E P E N L	1305.4	- (SEQ ID NO: 786)
983	F F H S P S E F E N L	1355.4	- (SEQ ID NO: 787)
984	F F H S P S E Y E N L	1371.4	- (SEQ ID NO: 788)
985	F F H S P S E W E N L	1394.5	- (SEQ ID NO: 789)
987	F F H S P S N P E N L	1290.5	- (SEQ ID NO: 790)
988	F F H S P S N F E N L	1340.5	- (SEQ ID NO: 791)
989	F F H S P S N Y E N L	1356.5	- (SEQ ID NO: 792)
990	F F H S P S N W E N L	1379.6	- (SEQ ID NO: 793)
992	F F H S P S Q P E N L	1304.5	- (SEQ ID NO: 794)
993	F F H S P S Q F E N L	1354.5	- (SEQ ID NO: 795)
994	F F H S P S Q Y E N L	1370.5	- (SEQ ID NO: 796)
995	F F H S P S Q W E N L	1393.6	- (SEQ ID NO: 797)
997	F F H S P S H P E N L	1313.5	- (SEQ ID NO: 798)
998	F F H S P S H F E N L	1363.5	- (SEQ ID NO: 799)
999	F F H S P S H Y E N L	1379.5	- (SEQ ID NO: 800)
1000	F F H S P S H W E N L	1402.6	- (SEQ ID NO: 801)
1002	F F N S P S M P E N L	1284.6	- (SEQ ID NO: 802)
1003	F F N S P S M F E N L	1334.6	- (SEQ ID NO: 803)
1004	F F N S P S M Y E N L	1350.6	- (SEQ ID NO: 804)
1005	F F N S P S M W E N L	1373.7	- (SEQ ID NO: 805)
1007	F F N S P S F P E N L	1300.5	- (SEQ ID NO: 806)

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1012	F F N S P S Y P E N L	1356.5	(SEQ ID NO: 810)

1013 F F N S P S Y F E N L 1366.5 - (SEQ ID NO: 811)

1014 F F N S P S Y Y E N L 1382.5 - (SEQ ID NO: 812)

1015 F F N S P S Y W E N L 1405.6 - (SEQ ID NO: 813)

1017 F F N S P S D P E N L 1268.4 - (SEQ ID NO: 814)

1018 F F N S P S D F E N L 1318.4 - (SEQ ID NO: 815)

1019 F F N S P S D Y E N L 1334.4 - (SEQ ID NO: 816)

1020 F F N S P S D W E N L 1357.5 - (SEQ ID NO: 817)

1022 F F N S P S E P E N L 1282.4 - (SEQ ID NO: 818)

1023 F F N S P S E F E N L 1332.4 - (SEQ ID NO: 819)

1024 F F N S P S E Y E N L 1348.4 - (SEQ ID NO: 820)

1025 F F N S P S E W E N L 1371.5 - (SEQ ID NO: 821)

1027 F F N S P S N P E N L 1267.5 - (SEQ ID NO: 822)

1028 F F N S P S N F E N L 1317.5 - (SEQ ID NO: 823)

1029 F F N S P S N Y E N L 1333.5 - (SEQ ID NO: 824)

1030 F F N S P S N W E N L 1356.6 - (SEQ ID NO: 825)

1032 F F N S P S Q P E N L 1281.5 - (SEQ ID NO: 826)

1033 F F N S P S Q F E N L 1331.5 - (SEQ ID NO: 827)

1034 F F N S P S Q Y E N L 1347.5 - (SEQ ID NO: 828)

1035 F F N S P S Q W E N L 1370.6 - (SEQ ID NO: 829)

1037 F F N S P S H P E N L 1290.5 - (SEQ ID NO: 830)

1038 F F N S P S H F E N L 1340.5 - (SEQ ID NO: 831)

1039 F F N S P S H Y E N L 1356.5 - (SEQ ID NO: 832)

1040 F F N S P S H W E N L 1379.6 - (SEQ ID NO: 833)

1042 F F G S P S M P E N L 1227.5 - (SEQ ID NO: 834)

1043 F F G S P S M F E N L 1277.5 - (SEQ ID NO: 835)

1044 F F G S P S M Y E N L 1293.5 - (SEQ ID NO: 836)

1045 F F G S P S M W E N L 1316.6 - (SEQ ID NO: 837)

1047 F F G S P S F P E N L 1243.4 - (SEQ ID NO: 838)

1048 F F G S P S F F E N L 1293.4 - (SEQ ID NO: 839)

1049 F F G S P S F Y E N L 1309.4 - (SEQ ID NO: 840)

1050 F F G S P S F W E N L 1332.5 - (SEQ ID NO: 841)

1052 F F G S P S Y P E N L 1259.4 - (SEQ ID NO: 842)

1053 F F G S P S Y F E N L 1309.4 - (SEQ ID NO: 843)

[illegible]

[illegible]

1058 F F G S P S D F E N L 1261.5 (SEQ ID NO: 847)

1059 F F G S P S D Y E N L 1277.3	-	(SEQ ID NO: 848)
1060 F F G S P S D W E N L 1300.4	-	(SEQ ID NO: 849)
1062 F F G S P S E P E N L 1225.3	-	(SEQ ID NO: 850)
1063 F F G S P S E F E N L 1275.3	-	(SEQ ID NO: 851)
1064 F F G S P S E Y E N L 1291.3	-	(SEQ ID NO: 852)
1065 F F G S P S E W E N L 1314.4	-	(SEQ ID NO: 853)
1067 F F G S P S N P E N L 1210.4	-	(SEQ ID NO: 854)
1068 F F G S P S N F E N L 1260.4	-	(SEQ ID NO: 855)
1069 F F G S P S N Y E N L 1276.4	-	(SEQ ID NO: 856)
1070 F F G S P S N W E N L 1299.5	-	(SEQ ID NO: 857)
1072 F F G S P S Q P E N L 1224.4	-	(SEQ ID NO: 858)
1073 F F G S P S Q F E N L 1274.4	-	(SEQ ID NO: 859)
1074 F F G S P S Q Y E N L 1290.4	-	(SEQ ID NO: 860)
1075 F F G S P S Q W E N L 1313.5	-	(SEQ ID NO: 861)
1077 F F G S P S H P E N L 1233.4	-	(SEQ ID NO: 862)
1078 F F G S P S H F E N L 1283.4	-	(SEQ ID NO: 863)
1079 F F G S P S H Y E N L 1299.4	-	(SEQ ID NO: 864)
1080 F F G S P S H W E N L 1322.5	-	(SEQ ID NO: 865)
1082 F F A S P S M P E N L 1241.5	-	(SEQ ID NO: 866)
1083 F F A S P S M F E N L 1291.5	-	(SEQ ID NO: 867)
1084 F F A S P S M Y E N L 1307.5	-	(SEQ ID NO: 868)
1085 F F A S P S M W E N L 1330.6	-	(SEQ ID NO: 869)
1087 F F A S P S F P E N L 1257.4	-	(SEQ ID NO: 870)
1088 F F A S P S F F E N L 1307.4	-	(SEQ ID NO: 871)
1089 F F A S P S F Y E N L 1323.4	-	(SEQ ID NO: 872)
1090 F F A S P S F W E N L 1346.5	-	(SEQ ID NO: 873)
1092 F F A S P S Y P E N L 1273.4	-	(SEQ ID NO: 874)
1093 F F A S P S Y F E N L 1323.4	-	(SEQ ID NO: 875)
1094 F F A S P S Y Y E N L 1339.4	-	(SEQ ID NO: 876)
1095 F F A S P S Y W E N L 1362.5	-	(SEQ ID NO: 877)
1097 F F A S P S D P E N L 1225.3	-	(SEQ ID NO: 878)
1098 F F A S P S D F E N L 1275.3	-	(SEQ ID NO: 879)
1099 F F A S P S D Y E N L 1291.3	-	(SEQ ID NO: 880)
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
1104 F F A S P S E Y E N L 1305.3		(SEQ ID NO: 884)

1105 F F A S P S E W E N L 1328.4	-	(SEQ ID NO: 885)
1107 F F A S P S N P E N L 1224.4	-	(SEQ ID NO: 886)
1108 F F A S P S N F E N L 1274.4	-	(SEQ ID NO: 887)
1109 F F A S P S N Y E N L 1290.4	-	(SEQ ID NO: 888)
1110 F F A S P S N W E N L 1313.5	-	(SEQ ID NO: 889)
1112 F F A S P S Q P E N L 1238.4	-	(SEQ ID NO: 890)
1113 F F A S P S Q F E N L 1288.4	-	(SEQ ID NO: 891)
1114 F F A S P S Q Y E N L 1304.4	-	(SEQ ID NO: 892)
1115 F F A S P S Q W E N L 1327.5	-	(SEQ ID NO: 893)
1117 F F A S P S H P E N L 1247.4	-	(SEQ ID NO: 894)
1118 F F A S P S H F E N L 1297.4	-	(SEQ ID NO: 895)
1119 F F A S P S H Y E N L 1313.4	-	(SEQ ID NO: 896)
1120 F F A S P S H W E N L 1336.5	-	(SEQ ID NO: 897)
1122 W Y R S P S M P E N L 1381.7	+	(SEQ ID NO: 898)
1123 W Y R S P S M F E N L 1431.7	+	(SEQ ID NO: 899)
1124 W Y R S P S M Y E N L 1447.7	++	(SEQ ID NO: 900)
1125 W Y R S P S M W E N L 1470.8	++	(SEQ ID NO: 901)
[redacted]	++	(SEQ ID NO: 902)
	++	(SEQ ID NO: 903)
	+++	(SEQ ID NO: 904)
	++	(SEQ ID NO: 905)
1132 W Y R S P S Y P E N L 1413.6	++	(SEQ ID NO: 906)
1133 W Y R S P S Y F E N L 1463.6	+	(SEQ ID NO: 907)
1134 W Y R S P S Y Y E N L 1479.6	++	(SEQ ID NO: 908)
1135 W Y R S P S Y W E N L 1502.7	+	(SEQ ID NO: 909)
1137 W Y R S P S D P E N L 1365.5	-	(SEQ ID NO: 910)
1138 W Y R S P S D F E N L 1415.5	-	(SEQ ID NO: 911)
1139 W Y R S P S D Y E N L 1431.5	-	(SEQ ID NO: 912)
1140 W Y R S P S D W E N L 1454.6	-	(SEQ ID NO: 913)
1142 W Y R S P S E P E N L 1379.5	-	(SEQ ID NO: 914)
1143 W Y R S P S E F E N L 1429.5	-	(SEQ ID NO: 915)
1144 W Y R S P S E Y E N L 1445.5	-	(SEQ ID NO: 916)
1145 W Y R S P S E W E N L 1468.6	-	(SEQ ID NO: 917)
[illegible]	[illegible]	[illegible]
1150 W Y R S P S N W E N L 1453.[illegible]		(SEQ ID NO: 921)

1152 W Y R S P S Q P E N L 1378.6	-	(SEQ ID NO: 922)
1153 W Y R S P S Q F E N L 1428.6	-	(SEQ ID NO: 923)
1154 W Y R S P S Q Y E N L 1444.6	-	(SEQ ID NO: 924)
1155 W Y R S P S Q W E N L 1467.7	-	(SEQ ID NO: 925)
1157 W Y R S P S H P E N L 1387.6	-	(SEQ ID NO: 926)
1158 W Y R S P S H F E N L 1437.6	-	(SEQ ID NO: 927)
1159 W Y R S P S H Y E N L 1453.6	-	(SEQ ID NO: 928)
1160 W Y R S P S H W E N L 1476.7	-	(SEQ ID NO: 929)
1162 W Y S S P S M P E N L 1313.4	-	(SEQ ID NO: 930)
1163 W Y S S P S M F E N L 1363.4	-	(SEQ ID NO: 931)
1164 W Y S S P S M Y E N L 1379.4	-	(SEQ ID NO: 932)
1165 W Y S S P S M W E N L 1402.5	-	(SEQ ID NO: 933)
1167 W Y S S P S F P E N L 1329.3	-	(SEQ ID NO: 934)
1168 W Y S S P S F F E N L 1379.3	-	(SEQ ID NO: 935)
1169 W Y S S P S F Y E N L 1395.3	-	(SEQ ID NO: 936)
1170 W Y S S P S F W E N L 1418.4	-	(SEQ ID NO: 937)
1172 W Y S S P S Y P E N L 1345.3	-	(SEQ ID NO: 938)
1173 W Y S S P S Y F E N L 1395.3	-	(SEQ ID NO: 939)
1174 W Y S S P S Y Y E N L 1411.3	-	(SEQ ID NO: 940)
1175 W Y S S P S Y W E N L 1434.4	-	(SEQ ID NO: 941)
1177 W Y S S P S D P E N L 1297.2	-	(SEQ ID NO: 942)
1178 W Y S S P S D F E N L 1347.2	-	(SEQ ID NO: 943)
1179 W Y S S P S D Y E N L 1363.2	-	(SEQ ID NO: 944)
1180 W Y S S P S D W E N L 1386.3	-	(SEQ ID NO: 945)
1182 W Y S S P S E P E N L 1311.2	-	(SEQ ID NO: 946)
1183 W Y S S P S E F E N L 1361.2	-	(SEQ ID NO: 947)
1184 W Y S S P S E Y E N L 1377.2	-	(SEQ ID NO: 948)
1185 W Y S S P S E W E N L 1400.3	-	(SEQ ID NO: 949)
1187 W Y S S P S N P E N L 1296.3	-	(SEQ ID NO: 950)
1188 W Y S S P S N F E N L 1346.3	-	(SEQ ID NO: 951)
1189 W Y S S P S N Y E N L 1362.3	-	(SEQ ID NO: 952)
1190 W Y S S P S N W E N L 1385.4	-	(SEQ ID NO: 953)
1192 W Y S S P S Q P E N L 1310.3	-	(SEQ ID NO: 954)
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1197 W Y S S P S H P E N L 1319.3		(SEQ ID NO: 958)

1198 W Y S S P S H F E N L 1369.3	-	(SEQ ID NO: 959)
1199 W Y S S P S H Y E N L 1385.3	-	(SEQ ID NO: 960)
1200 W Y S S P S H W E N L 1408.4	-	(SEQ ID NO: 961)
1202 W Y T S P S M P E N L 1326.6	·	(SEQ ID NO: 962)
1203 W Y T S P S M F E N L 1376.6	·	(SEQ ID NO: 963)
1204 W Y T S P S M Y E N L 1392.6	·	(SEQ ID NO: 964)
1205 W Y T S P S M W E N L 1415.7	·	(SEQ ID NO: 965)
1207 W Y T S P S F P E N L 1342.5	·	(SEQ ID NO: 966)
1208 W Y T S P S F F E N L 1392.5	+	(SEQ ID NO: 967)
1209 W Y T S P S F Y E N L 1408.5	·	(SEQ ID NO: 968)
1210 W Y T S P S F W E N L 1431.6	·	(SEQ ID NO: 969)
1212 W Y T S P S Y P E N L 1358.5	+ ·	(SEQ ID NO: 970)
1213 W Y T S P S Y F E N L 1408.5	+	(SEQ ID NO: 971)
1214 W Y T S P S Y Y E N L 1424.5	+	(SEQ ID NO: 972)
1215 W Y T S P S Y W E N L 1447.6	+	(SEQ ID NO: 973)
1217 W Y T S P S D P E N L 1310.4	-	(SEQ ID NO: 974)
1218 W Y T S P S D F E N L 1360.4	-	(SEQ ID NO: 975)
1219 W Y T S P S D Y E N L 1376.4	-	(SEQ ID NO: 976)
1220 W Y T S P S D W E N L 1399.5	-	(SEQ ID NO: 977)
1222 W Y T S P S E P E N L 1324.4	-	(SEQ ID NO: 978)
1223 W Y T S P S E F E N L 1374.4	-	(SEQ ID NO: 979)
1224 W Y T S P S E Y E N L 1390.4	-	(SEQ ID NO: 980)
1225 W Y T S P S E W E N L 1413.5	-	(SEQ ID NO: 981)
1227 W Y T S P S N P E N L 1309.5	-	(SEQ ID NO: 982)
1228 W Y T S P S N F E N L 1359.5	-	(SEQ ID NO: 983)
1229 W Y T S P S N Y E N L 1375.5	-	(SEQ ID NO: 984)
1230 W Y T S P S N W E N L 1398.6	-	(SEQ ID NO: 985)
1232 W Y T S P S Q P E N L 1323.5	-	(SEQ ID NO: 986)
1233 W Y T S P S Q F E N L 1373.5	-	(SEQ ID NO: 987)
1234 W Y T S P S Q Y E N L 1389.5	-	(SEQ ID NO: 988)
1235 W Y T S P S Q W E N L 1412.6	-	(SEQ ID NO: 989)
1237 W Y T S P S H P E N L 1332.5	·	(SEQ ID NO: 990)
1238 W Y T S P S H F E N L 1382.5	·	(SEQ ID NO: 991)
1239 W Y T S P S H Y E N L 1398.5		
1240 W Y T S P S H W E N L 1421.6		
1242 W Y H S P S M P E N L 1342.5		
1243 W Y H S P S M F E N L 1392.6		(SEQ ID NO: 992)

1244 W Y H S P S M Y E N L 1428.7	-	(SEQ ID NO: 996)
1245 W Y H S P S M W E N L 1451.8	-	(SEQ ID NO: 997)
1247 W Y H S P S F P E N L 1378.6	-	(SEQ ID NO: 998)
1248 W Y H S P S F F E N L 1428.6	-	(SEQ ID NO: 999)
1249 W Y H S P S F Y E N L 1444 6	-	(SEQ ID NO: 1000)
1250 W Y H S P S F W E N L 1467.7	-	(SEQ ID NO: 1001)
1252 W Y H S P S Y P E N L 1394 6	-	(SEQ ID NO: 1002)
1253 W Y H S P S Y F E N L 1444 6	-	(SEQ ID NO: 1003)
1254 W Y H S P S Y Y E N L 1460.6	-	(SEQ ID NO: 1004)
1255 W Y H S P S Y W E N L 1483 7	-	(SEQ ID NO: 1005)
1257 W Y H S P S D P E N L 1346.5	-	(SEQ ID NO: 1006)
1258 W Y H S P S D F E N L 1396 5	-	(SEQ ID NO: 1007)
1259 W Y H S P S D Y E N L 1412.5	-	(SEQ ID NO: 1008)
1260 W Y H S P S D W E N L 1435 6	-	(SEQ ID NO: 1009)
1262 W Y H S P S E P E N L 1360.5	-	(SEQ ID NO: 1010)
1263 W Y H S P S E F E N L 1410.5	-	(SEQ ID NO: 1011)
1264 W Y H S P S E Y E N L 1426.5	-	(SEQ ID NO: 1012)
1265 W Y H S P S E W E N L 1449.6	-	(SEQ ID NO: 1013)
1267 W Y H S P S N P E N L 1345.6	-	(SEQ ID NO: 1014)
1268 W Y H S P S N F E N L 1395.6	-	(SEQ ID NO: 1015)
1269 W Y H S P S N Y E N L 1411.6	-	(SEQ ID NO: 1016)
1270 W Y H S P S N W E N L 1434 7	-	(SEQ ID NO: 1017)
1272 W Y H S P S Q P E N L 1359.6	-	(SEQ ID NO: 1018)
1273 W Y H S P S Q F E N L 1409.6	-	(SEQ ID NO: 1019)
1274 W Y H S P S Q Y E N L 1425.6	-	(SEQ ID NO: 1020)
1275 W Y H S P S Q W E N L 1448.7	-	(SEQ ID NO: 1021)
1277 W Y H S P S H P E N L 1368.6	-	(SEQ ID NO: 1022)
1278 W Y H S P S H F E N L 1418.6	-	(SEQ ID NO: 1023)
1279 W Y H S P S H Y E N L 1434.6	-	(SEQ ID NO: 1024)
1280 W Y H S P S H W E N L 1457.7	-	(SEQ ID NO: 1025)
1282 W Y N S P S M P E N L 1339.7	-	(SEQ ID NO: 1026)
1283 W Y N S P S M F E N L 1389.7	-	(SEQ ID NO: 1027)
1284 W Y N S P S M Y E N L 1405.7	-	(SEQ ID NO: 1028)
[illegible]	[illegible]	[illegible]
1289 W Y N S P S E Y E N L 1421.6		(SEQ ID NO: 1032)

1290 W Y N S P S F W E N L 1444.7	-	(SEQ ID NO: 1033)
1292 W Y N S P S Y P E N L 1371.6	-	(SEQ ID NO: 1034)
1293 W Y N S P S Y F E N L 1421.6	-	(SEQ ID NO: 1035)
1294 W Y N S P S Y Y E N L 1437.6	-	(SEQ ID NO: 1036)
1295 W Y N S P S Y W E N L 1460.7	-	(SEQ ID NO: 1037)
1297 W Y N S P S D P E N L 1323 5	-	(SEQ ID NO: 1038)
1298 W Y N S P S D F E N L 1373 5	-	(SEQ ID NO: 1039)
1299 W Y N S P S D Y E N L 1389.5	-	(SEQ ID NO: 1040)
1300 W Y N S P S D W E N L 1412.6	-	(SEQ ID NO: 1041)
1302 W Y N S P S E P E N L 1337.5	-	(SEQ ID NO: 1042)
1303 W Y N S P S E F E N L 1387.5	-	(SEQ ID NO: 1043)
1304 W Y N S P S E Y E N L 1403.5	-	(SEQ ID NO: 1044)
1305 W Y N S P S E W E N L 1426.6	-	(SEQ ID NO: 1045)
1307 W Y N S P S N P E N L 1322 6	-	(SEQ ID NO: 1046)
1308 W Y N S P S N F E N L 1372 6	-	(SEQ ID NO: 1047)
1309 W Y N S P S N Y E N L 1388.6	-	(SEQ ID NO: 1048)
1310 W Y N S P S N W E N L 1411 7	-	(SEQ ID NO: 1049)
1312 W Y N S P S Q P E N L 1336 6	-	(SEQ ID NO: 1050)
1313 W Y N S P S Q F E N L 1386.6	-	(SEQ ID NO: 1051)
1314 W Y N S P S Q Y E N L 1402.6	-	(SEQ ID NO: 1052)
1315 W Y N S P S Q W E N L 1425.7	-	(SEQ ID NO: 1053)
1317 W Y N S P S H P E N L 1345 6	-	(SEQ ID NO: 1054)
1318 W Y N S P S H F E N L 1395 6	-	(SEQ ID NO: 1055)
1319 W Y N S P S H Y E N L 1411.6	-	(SEQ ID NO: 1056)
1320 W Y N S P S H W E N L 1434 7	-	(SEQ ID NO: 1057)
1322 W Y G S P S M P E N L 1282.6	-	(SEQ ID NO: 1058)
1323 W Y G S P S M F E N L 1332.6	-	(SEQ ID NO: 1059)
1324 W Y G S P S M Y E N L 1348.6	-	(SEQ ID NO: 1060)
1325 W Y G S P S M W E N L 1371.7	-	(SEQ ID NO: 1061)
1327 W Y G S P S F P E N L 1298.5	-	(SEQ ID NO: 1062)
1328 W Y G S P S F F E N L 1348.5	-	(SEQ ID NO: 1063)
1329 W Y G S P S F Y E N L 1364 5	-	(SEQ ID NO: 1064)
1330 W Y G S P S F W E N L 1387.6	-	(SEQ ID NO: 1065)

1333 W Y G S P S Y W E N L 1401.6 (SEQ ID NO: 1069)

1337	W Y G S P S D P E N L	1266.4	- (SEQ ID NO: 1070)
1338	W Y G S P S D F E N L	1316.4	- (SEQ ID NO: 1071)
1339	W Y G S P S D Y E N L	1332.4	- (SEQ ID NO: 1072)
1340	W Y G S P S D W E N L	1355.5	- (SEQ ID NO: 1073)
1342	W Y G S P S E P E N L	1280.4	- (SEQ ID NO: 1074)
1343	W Y G S P S E F E N L	1330.4	- (SEQ ID NO: 1075)
1344	W Y G S P S E Y E N L	1346.4	- (SEQ ID NO: 1076)
1345	W Y G S P S E W E N L	1369.5	- (SEQ ID NO: 1077)
1347	W Y G S P S N P E N L	1265.5	- (SEQ ID NO: 1078)
1348	W Y G S P S N F E N L	1315.5	- (SEQ ID NO: 1079)
1349	W Y G S P S N Y E N L	1331.5	- (SEQ ID NO: 1080)
1350	W Y G S P S N W E N L	1354.6	- (SEQ ID NO: 1081)
1352	W Y G S P S Q P E N L	1279.5	- (SEQ ID NO: 1082)
1353	W Y G S P S Q F E N L	1329.5	- (SEQ ID NO: 1083)
1354	W Y G S P S Q Y E N L	1345.5	- (SEQ ID NO: 1084)
1355	W Y G S P S Q W E N L	1368.6	- (SEQ ID NO: 1085)
1357	W Y G S P S H P E N L	1288.5	- (SEQ ID NO: 1086)
1358	W Y G S P S H F E N L	1338.5	- (SEQ ID NO: 1087)
1359	W Y G S P S H Y E N L	1354.5	- (SEQ ID NO: 1088)
1360	W Y G S P S H W E N L	1377.6	- (SEQ ID NO: 1089)
1362	W Y A S P S M P E N L	1296.6	- (SEQ ID NO: 1090)
1363	W Y A S P S M F E N L	1346.6	- (SEQ ID NO: 1091)
1364	W Y A S P S M Y E N L	1362.6	- (SEQ ID NO: 1092)
1365	W Y A S P S M W E N L	1385.7	- (SEQ ID NO: 1093)
1367	W Y A S P S F P E N L	1312.5	- (SEQ ID NO: 1094)
1368	W Y A S P S F F E N L	1362.5	- (SEQ ID NO: 1095)
1369	W Y A S P S F Y E N L	1378.5	- (SEQ ID NO: 1096)
1370	W Y A S P S F W E N L	1401.6	- (SEQ ID NO: 1097)
1372	W Y A S P S Y P E N L	1328.5	- (SEQ ID NO: 1098)
1373	W Y A S P S Y F E N L	1378.5	- (SEQ ID NO: 1099)
1374	W Y A S P S Y Y E N L	1394.5	- (SEQ ID NO: 1100)
1375	W Y A S P S Y W E N L	1417.6	- (SEQ ID NO: 1101)
1377	W Y A S P S D P E N L	1280.4	- (SEQ ID NO: 1102)
[illegible]			
1382	W Y A S P S E P E N L	1294.4	(SEQ ID NO: 1106)

1383 W Y A S P S E F E N L 1344.4	-	(SEQ ID NO: 1107)
1384 W Y A S P S E Y E N L 1360.4	-	(SEQ ID NO: 1108)
1385 W Y A S P S E W E N L 1383.5	-	(SEQ ID NO: 1109)
1387 W Y A S P S N P E N L 1279.5	-	(SEQ ID NO: 1110)
1388 W Y A S P S N F E N L 1329.5	-	(SEQ ID NO: 1111)
1389 W Y A S P S N Y E N L 1345.5	-	(SEQ ID NO: 1112)
1390 W Y A S P S N W E N L 1368.6	-	(SEQ ID NO: 1113)
1392 W Y A S P S Q P E N L 1293.5	-	(SEQ ID NO: 1114)
1393 W Y A S P S Q F E N L 1343.5	-	(SEQ ID NO: 1115)
1394 W Y A S P S Q Y E N L 1359.5	-	(SEQ ID NO: 1116)
1395 W Y A S P S Q W E N L 1382.6	-	(SEQ ID NO: 1117)
1397 W Y A S P S H P E N L 1302.5	-	(SEQ ID NO: 1118)
1398 W Y A S P S H F E N L 1352.5	-	(SEQ ID NO: 1119)
1399 W Y A S P S H Y E N L 1368.5	-	(SEQ ID NO: 1120)
1400 W Y A S P S H W E N L 1391.6	-	(SEQ ID NO: 1121)
1402 W F R S P S M P E N L 1365.7	-	(SEQ ID NO: 1122)
1403 W F R S P S M F E N L 1415.7	-	(SEQ ID NO: 1123)
1404 W F R S P S M Y E N L 1431.7	-	(SEQ ID NO: 1124)
1405 W F R S P S M W E N L 1454.8	-	(SEQ ID NO: 1125)
1407 W F R S P S F P E N L 1381.6	-	(SEQ ID NO: 1126)
1408 W F R S P S F F E N L 1431.6	-	(SEQ ID NO: 1127)
1409 W F R S P S F Y E N L 1447.6	-	(SEQ ID NO: 1128)
1410 W F R S P S F W E N L 1470.7	-	(SEQ ID NO: 1129)
1412 W F R S P S Y P E N L 1397.6	-	(SEQ ID NO: 1130)
1413 W F R S P S Y F E N L 1447.6	-	(SEQ ID NO: 1131)
1414 W F R S P S Y Y E N L 1463.6	-	(SEQ ID NO: 1132)
1415 W F R S P S Y W E N L 1486.7	-	(SEQ ID NO: 1133)
1417 W F R S P S D P E N L 1349.5	-	(SEQ ID NO: 1134)
1418 W F R S P S D F E N L 1399.5	-	(SEQ ID NO: 1135)
1419 W F R S P S D Y E N L 1415.5	-	(SEQ ID NO: 1136)
1420 W F R S P S D W E N L 1438.6	-	(SEQ ID NO: 1137)
1422 W F R S P S E P E N L 1363.5	-	(SEQ ID NO: 1138)
1423 W F R S P S E F E N L 1413.5	-	(SEQ ID NO: 1139)
[illegible]	[illegible]	[illegible]
1425 W F R S P S N F E N L 1398.6	-	(SEQ ID NO: 1141)

1429 W F R S P S N Y E N L 1414.6	-	(SEQ ID NO: 1144)
1430 W F R S P S N W E N L 1437.7	-	(SEQ ID NO: 1145)
1432 W F R S P S Q P E N L 1362.6	-	(SEQ ID NO: 1146)
1433 W F R S P S Q F E N L 1412.6	-	(SEQ ID NO: 1147)
1434 W F R S P S Q Y E N L 1428.6	-	(SEQ ID NO: 1148)
1435 W F R S P S Q W E N L 1451.7	-	(SEQ ID NO: 1149)
1437 W F R S P S H P E N L 1371.6	-	(SEQ ID NO: 1150)
1438 W F R S P S H F E N L 1421.6	-	(SEQ ID NO: 1151)
1439 W F R S P S H Y E N L 1437.6	-	(SEQ ID NO: 1152)
1440 W F R S P S H W E N L 1460.7	-	(SEQ ID NO: 1153)
1442 W F S S P S M P E N L 1297.4	-	(SEQ ID NO: 1154)
1443 W F S S P S M F E N L 1347.4	-	(SEQ ID NO: 1155)
1444 W F S S P S M Y E N L 1363.4	-	(SEQ ID NO: 1156)
1445 W F S S P S M W E N L 1386.5	-	(SEQ ID NO: 1157)
1447 W F S S P S F P E N L 1313.3	-	(SEQ ID NO: 1158)
1448 W F S S P S F F E N L 1363.3	-	(SEQ ID NO: 1159)
1449 W F S S P S F Y E N L 1379.3	-	(SEQ ID NO: 1160)
1450 W F S S P S F W E N L 1402.4	-	(SEQ ID NO: 1161)
1452 W F S S P S Y P E N L 1329.3	-	(SEQ ID NO: 1162)
1453 W F S S P S Y F E N L 1379.3	-	(SEQ ID NO: 1163)
1454 W F S S P S Y Y E N L 1395.3	-	(SEQ ID NO: 1164)
1455 W F S S P S Y W E N L 1418.4	-	(SEQ ID NO: 1165)
1457 W F S S P S D P E N L 1281.2	-	(SEQ ID NO: 1166)
1458 W F S S P S D F E N L 1331.2	-	(SEQ ID NO: 1167)
1459 W F S S P S D Y E N L 1347.2	-	(SEQ ID NO: 1168)
1460 W F S S P S D W E N L 1370.3	-	(SEQ ID NO: 1169)
1462 W F S S P S E P E N L 1295.2	-	(SEQ ID NO: 1170)
1463 W F S S P S E F E N L 1345.2	-	(SEQ ID NO: 1171)
1464 W F S S P S E Y E N L 1361.2	-	(SEQ ID NO: 1172)
1465 W F S S P S E W E N L 1384.3	-	(SEQ ID NO: 1173)
1467 W F S S P S N P E N L 1280.3	-	(SEQ ID NO: 1174)
1468 W F S S P S N F E N L 1330.3	-	(SEQ ID NO: 1175)
1469 W F S S P S N Y E N L 1346.3	-	(SEQ ID NO: 1176)
1470 W F S S P S N W E N L 1369.4	-	(SEQ ID NO: 1177)

1474 W F S S P S Q Y E N L 1360.4 - (SEQ ID NO: 1180)

1475 W F S S P S Q W E N L 1383.4 - (SEQ ID NO: 1181)

1477 W F S S P S H P E N L 1303.3 - (SEQ ID NO: 1182)

1478 W F S S P S H F E N L 1353.3 - (SEQ ID NO: 1183)

1479 W F S S P S H Y E N L 1369.3 - (SEQ ID NO: 1184)

1480 W F S S P S H W E N L 1392.4 - (SEQ ID NO: 1185)

1482 W F T S P S M P E N L 1310.6 - (SEQ ID NO: 1186)

1483 W F T S P S M F E N L 1360.6 - (SEQ ID NO: 1187)

1484 W F T S P S M Y E N L 1376.6 - (SEQ ID NO: 1188)

1485 W F T S P S M W E N L 1399.7 - (SEQ ID NO: 1189)

1487 W F T S P S F P E N L 1326.5 - (SEQ ID NO: 1190)

1488 W F T S P S F F E N L 1376.5 - (SEQ ID NO: 1191)

1489 W F T S P S F Y E N L 1392.5 - (SEQ ID NO: 1192)

1490 W F T S P S F W E N L 1415.6 - (SEQ ID NO: 1193)

1492 W F T S P S Y P E N L 1342.5 - (SEQ ID NO: 1194)

1493 W F T S P S Y F E N L 1392.5 - (SEQ ID NO: 1195)

1494 W F T S P S Y Y E N L 1408.5 - (SEQ ID NO: 1196)

1495 W F T S P S Y W E N L 1431.6 - (SEQ ID NO: 1197)

1497 W F T S P S D P E N L 1294.4 - (SEQ ID NO: 1198)

1498 W F T S P S D F E N L 1344.4 - (SEQ ID NO: 1199)

1499 W F T S P S D Y E N L 1360.4 - (SEQ ID NO: 1200)

1500 W F T S P S D W E N L 1383.5 - (SEQ ID NO: 1201)

1502 W F T S P S E P E N L 1308.4 - (SEQ ID NO: 1202)

1503 W F T S P S E F E N L 1358.4 - (SEQ ID NO: 1203)

1504 W F T S P S E Y E N L 1374.4 - (SEQ ID NO: 1204)

1505 W F T S P S E W E N L 1397.5 - (SEQ ID NO: 1205)

1507 W F T S P S N P E N L 1293.5 - (SEQ ID NO: 1206)

1508 W F T S P S N F E N L 1343.5 - (SEQ ID NO: 1207)

1509 W F T S P S N Y E N L 1359.5 - (SEQ ID NO: 1208)

1510 W F T S P S N W E N L 1382.6 - (SEQ ID NO: 1209)

1512 W F T S P S Q P E N L 1307.5 - (SEQ ID NO: 1210)

1513 W F T S P S Q F E N L 1357.5 - (SEQ ID NO: 1211)

1514 W F T S P S Q Y E N L 1373.5 - (SEQ ID NO: 1212)

1515 W F T S P S Q W E N L 1396.6 - (SEQ ID NO: 1213)

[illegible]

[illegible]

1520 W F T S P S H W E N L 1405.6 (SEQ ID NO: 121[illegible])

1522 W F H S P S M P E N L 1346.7	-	(SEQ ID NO: 1218)
1523 W F H S P S M F E N L 1396.7	-	(SEQ ID NO: 1219)
1524 W F H S P S M Y E N L 1412.7	-	(SEQ ID NO: 1220)
1525 W F H S P S M W E N L 1435.8	-	(SEQ ID NO: 1221)
1527 W F H S P S F P E N L 1362.6	-	(SEQ ID NO: 1222)
1528 W F H S P S F F E N L 1412.6	-	(SEQ ID NO: 1223)
1529 W F H S P S F Y E N L 1428.6	-	(SEQ ID NO: 1224)
1530 W F H S P S F W E N L 1451.7	-	(SEQ ID NO: 1225)
1532 W F H S P S Y P E N L 1378.6	-	(SEQ ID NO: 1226)
1533 W F H S P S Y F E N L 1428.6	-	(SEQ ID NO: 1227)
1534 W F H S P S Y Y E N L 1444.6	-	(SEQ ID NO: 1228)
1535 W F H S P S Y W E N L 1467.7	-	(SEQ ID NO: 1229)
1537 W F H S P S D P E N L 1330.5	-	(SEQ ID NO: 1230)
1538 W F H S P S D F E N L 1380.5	-	(SEQ ID NO: 1231)
1539 W F H S P S D Y E N L 1396.5	-	(SEQ ID NO: 1232)
1540 W F H S P S D W E N L 1419.6	-	(SEQ ID NO: 1233)
1542 W F H S P S E P E N L 1344.5	-	(SEQ ID NO: 1234)
1543 W F H S P S E F E N L 1394.5	-	(SEQ ID NO: 1235)
1544 W F H S P S E Y E N L 1410.5	-	(SEQ ID NO: 1236)
1545 W F H S P S E W E N L 1433.6	-	(SEQ ID NO: 1237)
1547 W F H S P S N P E N L 1329.6	-	(SEQ ID NO: 1238)
1548 W F H S P S N F E N L 1379.6	-	(SEQ ID NO: 1239)
1549 W F H S P S N Y E N L 1395.6	-	(SEQ ID NO: 1240)
1550 W F H S P S N W E N L 1418.7	-	(SEQ ID NO: 1241)
1552 W F H S P S Q P E N L 1343.6	-	(SEQ ID NO: 1242)
1553 W F H S P S Q F E N L 1393.6	-	(SEQ ID NO: 1243)
1554 W F H S P S Q Y E N L 1409.6	-	(SEQ ID NO: 1244)
1555 W F H S P S Q W E N L 1432.7	-	(SEQ ID NO: 1245)
1557 W F H S P S H P E N L 1352.6	-	(SEQ ID NO: 1246)
1558 W F H S P S H F E N L 1402.6	-	(SEQ ID NO: 1247)
1559 W F H S P S H Y E N L 1418.6	-	(SEQ ID NO: 1248)
1560 W F H S P S H W E N L 1441.7	-	(SEQ ID NO: 1249)
1562 W F N S P S M P E N L 1323.7	-	(SEQ ID NO: 1250)

1567 W F N S P S F P E N L 1339.6 (SEQ ID NO: 1254)

1568	W F N S P S F F E N L	1389.6	- (SEQ ID NO: 1255)
1569	W F N S P S F Y E N L	1405.6	- (SEQ ID NO: 1256)
1570	W F N S P S F W E N L	1428.7	- (SEQ ID NO: 1257)
1572	W F N S P S Y P E N L	1355.6	- (SEQ ID NO: 1258)
1573	W F N S P S Y F E N L	1405.6	- (SEQ ID NO: 1259)
1574	W F N S P S Y Y E N L	1421.6	- (SEQ ID NO: 1260)
1575	W F N S P S Y W E N L	1444.7	- (SEQ ID NO: 1261)
1577	W F N S P S D P E N L	1307.5	- (SEQ ID NO: 1262)
1578	W F N S P S D F E N L	1357.5	- (SEQ ID NO: 1263)
1579	W F N S P S D Y E N L	1373.5	- (SEQ ID NO: 1264)
1580	W F N S P S D W E N L	1396.6	- (SEQ ID NO: 1265)
1582	W F N S P S E P E N L	1321.5	- (SEQ ID NO: 1266)
1583	W F N S P S E F E N L	1371.5	- (SEQ ID NO: 1267)
1584	W F N S P S E Y E N L	1387.5	- (SEQ ID NO: 1268)
1585	W F N S P S E W E N L	1410.6	- (SEQ ID NO: 1269)
1587	W F N S P S N P E N L	1306.6	- (SEQ ID NO: 1270)
1588	W F N S P S N F E N L	1356.6	- (SEQ ID NO: 1271)
1589	W F N S P S N Y E N L	1372.6	- (SEQ ID NO: 1272)
1590	W F N S P S N W E N L	1395.7	- (SEQ ID NO: 1273)
1592	W F N S P S Q P E N L	1320.6	- (SEQ ID NO: 1274)
1593	W F N S P S Q F E N L	1370.6	- (SEQ ID NO: 1275)
1594	W F N S P S Q Y E N L	1386.6	- (SEQ ID NO: 1276)
1595	W F N S P S Q W E N L	1409.7	- (SEQ ID NO: 1277)
1597	W F N S P S H P E N L	1329.6	- (SEQ ID NO: 1278)
1598	W F N S P S H F E N L	1379.6	- (SEQ ID NO: 1279)
1599	W F N S P S H Y E N L	1395.6	- (SEQ ID NO: 1280)
1600	W F N S P S H W E N L	1418.7	- (SEQ ID NO: 1281)
1602	W F G S P S M P E N L	1266.6	- (SEQ ID NO: 1282)
1603	W F G S P S M F E N L	1316.6	- (SEQ ID NO: 1283)
1604	W F G S P S M Y E N L	1332.6	- (SEQ ID NO: 1284)
1605	W F G S P S M W E N L	1355.7	- (SEQ ID NO: 1285)
1607	W F G S P S F P E N L	1282.5	- (SEQ ID NO: 1286)
1608	W F G S P S F F E N L	1332.5	- (SEQ ID NO: 1287)
[illegible]			

[illegible]	W F G S P S Y F E N L	[illegible]	(SEQ ID NO: 1291)

1614	W F G S P S Y Y E N L	1364.5	- (SEQ ID NO: 1292)
1615	W F G S P S Y W E N L	1387.6	- (SEQ ID NO: 1293)
1617	W F G S P S D P E N L	1250.4	- (SEQ ID NO: 1294)
1618	W F G S P S D F E N L	1300.4	- (SEQ ID NO: 1295)
1619	W F G S P S D Y E N L	1316.4	- (SEQ ID NO: 1296)
1620	W F G S P S D W E N L	1339.5	- (SEQ ID NO: 1297)
1622	W F G S P S E P E N L	1264.4	- (SEQ ID NO: 1298)
1623	W F G S P S E F E N L	1314.4	- (SEQ ID NO: 1299)
1624	W F G S P S E Y E N L	1330.4	- (SEQ ID NO: 1300)
1625	W F G S P S E W E N L	1353.5	- (SEQ ID NO: 1301)
1627	W F G S P S N P E N L	1249.5	- (SEQ ID NO: 1302)
1628	W F G S P S N F E N L	1299.5	- (SEQ ID NO: 1303)
1629	W F G S P S N Y E N L	1315.5	- (SEQ ID NO: 1304)
1630	W F G S P S N W E N L	1338.6	- (SEQ ID NO: 1305)
1632	W F G S P S Q P E N L	1263.5	- (SEQ ID NO: 1306)
1633	W F G S P S Q F E N L	1313.5	- (SEQ ID NO: 1307)
1634	W F G S P S Q Y E N L	1329.5	- (SEQ ID NO: 1308)
1635	W F G S P S Q W E N L	1352.6	- (SEQ ID NO: 1309)
1637	W F G S P S H P E N L	1272.5	- (SEQ ID NO: 1310)
1638	W F G S P S H F E N L	1322.5	- (SEQ ID NO: 1311)
1639	W F G S P S H Y E N L	1338.5	- (SEQ ID NO: 1312)
1640	W F G S P S H W E N L	1361.6	- (SEQ ID NO: 1313)
1642	W F A S P S M P E N L	1280.6	- (SEQ ID NO: 1314)
1643	W F A S P S M F E N L	1330.6	- (SEQ ID NO: 1315)
1644	W F A S P S M Y E N L	1346.6	- (SEQ ID NO: 1316)
1645	W F A S P S M W E N L	1369.7	- (SEQ ID NO: 1317)
1647	W F A S P S F P E N L	1296.5	- (SEQ ID NO: 1318)
1648	W F A S P S F F E N L	1346.5	- (SEQ ID NO: 1319)
1649	W F A S P S F Y E N L	1362.5	- (SEQ ID NO: 1320)
1650	W F A S P S F W E N L	1385.6	- (SEQ ID NO: 1321)
1652	W F A S P S Y P E N L	1312.5	- (SEQ ID NO: 1322)
1653	W F A S P S Y F E N L	1362.5	- (SEQ ID NO: 1323)
1654	W F A S P S Y Y E N L	1378.5	- (SEQ ID NO: 1324)

1659	W F A S P S D Y E N L	1330.4	(SEQ ID NO: 1328)

1660 W F A S P S D W E N L 1353.5	-	(SEQ ID NO: 1329)
1662 W F A S P S E P E N L 1278.4	-	(SEQ ID NO: 1330)
1663 W F A S P S E F E N L 1328.4	-	(SEQ ID NO: 1331)
1664 W F A S P S E Y E N L 1344.4	-	(SEQ ID NO: 1332)
1665 W F A S P S E W E N L 1367.5	-	(SEQ ID NO: 1333)
1667 W F A S P S N P E N L 1263.5	-	(SEQ ID NO: 1334)
1668 W F A S P S N F E N L 1313.5	-	(SEQ ID NO: 1335)
1669 W F A S P S N Y E N L 1329.5	-	(SEQ ID NO: 1336)
1670 W F A S P S N W E N L 1352.6	-	(SEQ ID NO: 1337)
1672 W F A S P S Q P E N L 1277.5	-	(SEQ ID NO: 1338)
1673 W F A S P S Q F E N L 1327.5	-	(SEQ ID NO: 1339)
1674 W F A S P S Q Y E N L 1343.5	-	(SEQ ID NO: 1340)
1675 W F A S P S Q W E N L 1366.6	-	(SEQ ID NO: 1341)
1677 W F A S P S H P E N L 1286.5	-	(SEQ ID NO: 1342)
1678 W F A S P S H F E N L 1336.5	-	(SEQ ID NO: 1343)
1679 W F A S P S H Y E N L 1352.5	-	(SEQ ID NO: 1344)
1680 W F A S P S H W E N L 1375.6	-	(SEQ ID NO: 1345)
1682 M Y R S P S M P E N L 1326.7	-	(SEQ ID NO: 1346)
1683 M Y R S P S M F E N L 1376.7	-	(SEQ ID NO: 1347)
1684 M Y R S P S M Y E N L 1392.7	-	(SEQ ID NO: 1348)
1685 M Y R S P S M W E N L 1415.8	-	(SEQ ID NO: 1349)
1687 M Y R S P S F P E N L 1342.6	-	(SEQ ID NO: 1350)
1688 M Y R S P S F F E N L 1392.6	-	(SEQ ID NO: 1351)
1689 M Y R S P S F Y E N L 1408.6	-	(SEQ ID NO: 1352)
1690 M Y R S P S F W E N L 1431.7	-	(SEQ ID NO: 1353)
1692 M Y R S P S Y P E N L 1358.6	-	(SEQ ID NO: 1354)
1693 M Y R S P S Y F E N L 1408.6	-	(SEQ ID NO: 1355)
1694 M Y R S P S Y Y E N L 1424.6	-	(SEQ ID NO: 1356)
1695 M Y R S P S Y W E N L 1447.7	-	(SEQ ID NO: 1357)
1697 M Y R S P S D P E N L 1310.5	-	(SEQ ID NO: 1358)
1698 M Y R S P S D F E N L 1360.5	-	(SEQ ID NO: 1359)
1699 M Y R S P S D Y E N L 1376.5	-	(SEQ ID NO: 1360)
1700 M Y R S P S D W E N L 1399.6	-	(SEQ ID NO: 1361)

[illegible] M Y R S P S E W E N L 1413.6 - (SEQ ID NO: 1362)

1707	M Y R S P S N P E N L	1309.6	- (SEQ ID NO: 1366)
1708	M Y R S P S N F E N L	1359.6	- (SEQ ID NO: 1367)
1709	M Y R S P S N Y E N L	1375.6	- (SEQ ID NO: 1368)
1710	M Y R S P S N W E N L	1398.7	- (SEQ ID NO: 1369)
1712	M Y R S P S Q P E N L	1323.6	- (SEQ ID NO: 1370)
1713	M Y R S P S Q F E N L	1373.6	- (SEQ ID NO: 1371)
1714	M Y R S P S Q Y E N L	1389.6	- (SEQ ID NO: 1372)
1715	M Y R S P S Q W E N L	1412.7	- (SEQ ID NO: 1373)
1717	M Y R S P S H P E N L	1332.6	- (SEQ ID NO: 1374)
1718	M Y R S P S H F E N L	1382.6	- (SEQ ID NO: 1375)
1719	M Y R S P S H Y E N L	1398.6	- (SEQ ID NO: 1376)
1720	M Y R S P S H W E N L	1421.7	- (SEQ ID NO: 1377)
1722	M Y S S P S M P E N L	1258.4	- (SEQ ID NO: 1378)
1723	M Y S S P S M F E N L	1308.4	- (SEQ ID NO: 1379)
1724	M Y S S P S M Y E N L	1324.4	- (SEQ ID NO: 1380)
1725	M Y S S P S M W E N L	1347.5	- (SEQ ID NO: 1381)
1727	M Y S S P S F P E N L	1274.3	- (SEQ ID NO: 1382)
1728	M Y S S P S F F E N L	1324.3	- (SEQ ID NO: 1383)
1729	M Y S S P S F Y E N L	1340.3	- (SEQ ID NO: 1384)
1730	M Y S S P S F W E N L	1363.4	- (SEQ ID NO: 1385)
1732	M Y S S P S Y P E N L	1290.3	- (SEQ ID NO: 1386)
1733	M Y S S P S Y F E N L	1340.3	- (SEQ ID NO: 1387)
1734	M Y S S P S Y Y E N L	1356.3	- (SEQ ID NO: 1388)
1735	M Y S S P S Y W E N L	1379.4	- (SEQ ID NO: 1389)
1737	M Y S S P S D P E N L	1242.2	- (SEQ ID NO: 1390)
1738	M Y S S P S D F E N L	1292.2	- (SEQ ID NO: 1391)
1739	M Y S S P S D Y E N L	1308.2	- (SEQ ID NO: 1392)
1740	M Y S S P S D W E N L	1331.3	- (SEQ ID NO: 1393)
1742	M Y S S P S E P E N L	1256.2	- (SEQ ID NO: 1394)
1743	M Y S S P S E F E N L	1306.2	- (SEQ ID NO: 1395)
1744	M Y S S P S E Y E N L	1322.2	- (SEQ ID NO: 1396)
1745	M Y S S P S E W E N L	1345.3	- (SEQ ID NO: 1397)
1747	M Y S S P S N P E N L	1241.3	- (SEQ ID NO: 1398)
[illegible]			

1752	M Y S S P S Q P E N L	1255.3	(SEQ ID NO: 1402)

1753	M Y S S P S Q F E N L	1305.3	- (SEQ ID NO: 1403)
1754	M Y S S P S Q Y E N L	1321.3	- (SEQ ID NO: 1404)
1755	M Y S S P S Q W E N L	1344.4	- (SEQ ID NO: 1405)
1757	M Y S S P S H P E N L	1264.3	- (SEQ ID NO: 1406)
1758	M Y S S P S H F E N L	1314.3	- (SEQ ID NO: 1407)
1759	M Y S S P S H Y E N L	1330.3	- (SEQ ID NO: 1408)
1760	M Y S S P S H W E N L	1353.4	- (SEQ ID NO: 1409)
1762	M Y T S P S M P E N L	1271.6	- (SEQ ID NO: 1410)
1763	M Y T S P S M F E N L	1321.6	- (SEQ ID NO: 1411)
1764	M Y T S P S M Y E N L	1337.6	- (SEQ ID NO: 1412)
1765	M Y T S P S M W E N L	1360.7	- (SEQ ID NO: 1413)
1767	M Y T S P S F P E N L	1287.5	- (SEQ ID NO: 1414)
1768	M Y T S P S F F E N L	1337.5	- (SEQ ID NO: 1415)
1769	M Y T S P S F Y E N L	1353.5	- (SEQ ID NO: 1416)
1770	M Y T S P S F W E N L	1376.6	- (SEQ ID NO: 1417)
1772	M Y T S P S Y P E N L	1303.5	- (SEQ ID NO: 1418)
1773	M Y T S P S Y F E N L	1353.5	- (SEQ ID NO: 1419)
1774	M Y T S P S Y Y E N L	1369.5	- (SEQ ID NO: 1420)
1775	M Y T S P S Y W E N L	1392.6	- (SEQ ID NO: 1421)
1777	M Y T S P S D P E N L	1255.4	- (SEQ ID NO: 1422)
1778	M Y T S P S D F E N L	1305.4	- (SEQ ID NO: 1423)
1779	M Y T S P S D Y E N L	1321.4	- (SEQ ID NO: 1424)
1780	M Y T S P S D W E N L	1344.5	- (SEQ ID NO: 1425)
1782	M Y T S P S E P E N L	1269.4	- (SEQ ID NO: 1426)
1783	M Y T S P S E F E N L	1319.4	- (SEQ ID NO: 1427)
1784	M Y T S P S E Y E N L	1335.4	- (SEQ ID NO: 1428)
1785	M Y T S P S E W E N L	1358.5	- (SEQ ID NO: 1429)
1787	M Y T S P S N P E N L	1254.5	- (SEQ ID NO: 1430)
1788	M Y T S P S N F E N L	1304.5	- (SEQ ID NO: 1431)
1789	M Y T S P S N Y E N L	1320.5	- (SEQ ID NO: 1432)
1790	M Y T S P S N W E N L	1343.6	- (SEQ ID NO: 1433)
1792	M Y T S P S Q P E N L	1268.5	- (SEQ ID NO: 1434)
1793	M Y T S P S Q F E N L	1318.5	- (SEQ ID NO: 1435)
[illegible]			

1798	M Y T S P S H T E N L	1327.5	(SEQ ID NO: 1439)

1799	M Y T S P S H Y E N L	1343.5	- (SEQ ID NO: 1440)
1800	M Y T S P S H W E N L	1366.6	- (SEQ ID NO: 1441)
1802	M Y H S P S M P E N L	1307.7	- (SEQ ID NO: 1442)
1803	M Y H S P S M F E N L	1357.7	- (SEQ ID NO: 1443)
1804	M Y H S P S M Y E N L	1373.7	- (SEQ ID NO: 1444)
1805	M Y H S P S M W E N L	1396.8	- (SEQ ID NO: 1445)
1807	M Y H S P S F P E N L	1323.6	- (SEQ ID NO: 1446)
1808	M Y H S P S F F E N L	1373.6	- (SEQ ID NO: 1447)
1809	M Y H S P S F Y E N L	1389.6	- (SEQ ID NO: 1448)
1810	M Y H S P S F W E N L	1412.7	- (SEQ ID NO: 1449)
1812	M Y H S P S Y P E N L	1339.6	- (SEQ ID NO: 1450)
1813	M Y H S P S Y F E N L	1389.6	- (SEQ ID NO: 1451)
1814	M Y H S P S Y Y E N L	1405.6	- (SEQ ID NO: 1452)
1815	M Y H S P S Y W E N L	1428.7	- (SEQ ID NO: 1453)
1817	M Y H S P S D P E N L	1291.5	- (SEQ ID NO: 1454)
1818	M Y H S P S D F E N L	1341.5	- (SEQ ID NO: 1455)
1819	M Y H S P S D Y E N L	1357.5	- (SEQ ID NO: 1456)
1820	M Y H S P S D W E N L	1380.6	- (SEQ ID NO: 1457)
1822	M Y H S P S E P E N L	1305.5	- (SEQ ID NO: 1458)
1823	M Y H S P S E F E N L	1355.5	- (SEQ ID NO: 1459)
1824	M Y H S P S E Y E N L	1371.5	- (SEQ ID NO: 1460)
1825	M Y H S P S E W E N L	1394.6	- (SEQ ID NO: 1461)
1827	M Y H S P S N P E N L	1290.6	- (SEQ ID NO: 1462)
1828	M Y H S P S N F E N L	1340.6	- (SEQ ID NO: 1463)
1829	M Y H S P S N Y E N L	1356.6	- (SEQ ID NO: 1464)
1830	M Y H S P S N W E N L	1379.7	- (SEQ ID NO: 1465)
1832	M Y H S P S Q P E N L	1304.6	- (SEQ ID NO: 1466)
1833	M Y H S P S Q F E N L	1354.6	- (SEQ ID NO: 1467)
1834	M Y H S P S Q Y E N L	1370.6	- (SEQ ID NO: 1468)
1835	M Y H S P S Q W E N L	1393.7	- (SEQ ID NO: 1469)
1837	M Y H S P S H P E N L	1313.6	- (SEQ ID NO: 1470)
1838	M Y H S P S H F E N L	1363.6	- (SEQ ID NO: 1471)
1839	M Y H S P S H Y E N L	1379.6	- (SEQ ID NO: 1472)

1844	M Y N S P S M Y E N L	1350.7	(SEQ ID NO: 1476)

1845 M Y N S P S M W E N L 1373.8	-	(SEQ ID NO: 1477)
1847 M Y N S P S F P E N L 1300.6	-	(SEQ ID NO: 1478)
1848 M Y N S P S F F E N L 1350.6	-	(SEQ ID NO: 1479)
1849 M Y N S P S F Y E N L 1366.6	-	(SEQ ID NO: 1480)
1850 M Y N S P S F W E N L 1389.7	-	(SEQ ID NO: 1481)
1852 M Y N S P S Y P E N L 1316.6	-	(SEQ ID NO: 1482)
1853 M Y N S P S Y F E N L 1366.6	-	(SEQ ID NO: 1483)
1854 M Y N S P S Y Y E N L 1382.6	-	(SEQ ID NO: 1484)
1855 M Y N S P S Y W E N L 1405.7	-	(SEQ ID NO: 1485)
1857 M Y N S P S D P E N L 1268.5	-	(SEQ ID NO: 1486)
1858 M Y N S P S D F E N L 1318.5	-	(SEQ ID NO: 1487)
1859 M Y N S P S D Y E N L 1334.5	-	(SEQ ID NO: 1488)
1860 M Y N S P S D W E N L 1357.6	-	(SEQ ID NO: 1489)
1862 M Y N S P S E P E N L 1282.5	-	(SEQ ID NO: 1490)
1863 M Y N S P S E F E N L 1332.5	-	(SEQ ID NO: 1491)
1864 M Y N S P S E Y E N L 1348.5	-	(SEQ ID NO: 1492)
1865 M Y N S P S E W E N L 1371.6	-	(SEQ ID NO: 1493)
1867 M Y N S P S N P E N L 1267.6	-	(SEQ ID NO: 1494)
1868 M Y N S P S N F E N L 1317.6	-	(SEQ ID NO: 1495)
1869 M Y N S P S N Y E N L 1333.6	-	(SEQ ID NO: 1496)
1870 M Y N S P S N W E N L 1356.7	-	(SEQ ID NO: 1497)
1872 M Y N S P S Q P E N L 1281.6	-	(SEQ ID NO: 1498)
1873 M Y N S P S Q F E N L 1331.6	-	(SEQ ID NO: 1499)
1874 M Y N S P S Q Y E N L 1347.6	-	(SEQ ID NO: 1500)
1875 M Y N S P S Q W E N L 1370.7	-	(SEQ ID NO: 1501)
1877 M Y N S P S H P E N L 1290.6	-	(SEQ ID NO: 1502)
1878 M Y N S P S H F E N L 1340.6	-	(SEQ ID NO: 1503)
1879 M Y N S P S H Y E N L 1356.6	-	(SEQ ID NO: 1504)
1880 M Y N S P S H W E N L 1379.7	-	(SEQ ID NO: 1505)
1882 M Y G S P S M P E N L 1227.6	-	(SEQ ID NO: 1506)
1883 M Y G S P S M F E N L 1277.6	-	(SEQ ID NO: 1507)
1884 M Y G S P S M Y E N L 1293.6	-	(SEQ ID NO: 1508)
1885 M Y G S P S M W E N L 1316.7	-	(SEQ ID NO: 1509)
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
1890 M Y G S P S E W E N L 1352.6		(SEQ ID NO: 1514)

1892	M Y G S P S Y P E N L	1259.5	- (SEQ ID NO: 1514)
1893	M Y G S P S Y F E N L	1309.5	- (SEQ ID NO: 1515)
1894	M Y G S P S Y Y E N L	1325.5	- (SEQ ID NO: 1516)
1895	M Y G S P S Y W E N L	1348.6	- (SEQ ID NO: 1517)
1897	M Y G S P S D P E N L	1211.4	- (SEQ ID NO: 1518)
1898	M Y G S P S D F E N L	1261.4	- (SEQ ID NO: 1519)
1899	M Y G S P S D Y E N L	1277.4	- (SEQ ID NO: 1520)
1900	M Y G S P S D W E N L	1300.5	- (SEQ ID NO: 1521)
1902	M Y G S P S E P E N L	1225.4	- (SEQ ID NO: 1522)
1903	M Y G S P S E F E N L	1275.4	- (SEQ ID NO: 1523)
1904	M Y G S P S E Y E N L	1291.4	- (SEQ ID NO: 1524)
1905	M Y G S P S E W E N L	1314.5	- (SEQ ID NO: 1525)
1907	M Y G S P S N P E N L	1210.5	- (SEQ ID NO: 1526)
1908	M Y G S P S N F E N L	1260.5	- (SEQ ID NO: 1527)
1909	M Y G S P S N Y E N L	1276.5	- (SEQ ID NO: 1528)
1910	M Y G S P S N W E N L	1299.6	- (SEQ ID NO: 1529)
1912	M Y G S P S Q P E N L	1224.5	- (SEQ ID NO: 1530)
1913	M Y G S P S Q F E N L	1274.5	- (SEQ ID NO: 1531)
1914	M Y G S P S Q Y E N L	1290.5	- (SEQ ID NO: 1532)
1915	M Y G S P S Q W E N L	1313.6	- (SEQ ID NO: 1533)
1917	M Y G S P S H P E N L	1233.5	- (SEQ ID NO: 1534)
1918	M Y G S P S H F E N L	1283.5	- (SEQ ID NO: 1535)
1919	M Y G S P S H Y E N L	1299.5	- (SEQ ID NO: 1536)
1920	M Y G S P S H W E N L	1322.6	- (SEQ ID NO: 1537)
1922	M Y A S P S M P E N L	1241.6	- (SEQ ID NO: 1538)
1923	M Y A S P S M F E N L	1291.6	- (SEQ ID NO: 1539)
1924	M Y A S P S M Y E N L	1307.6	- (SEQ ID NO: 1540)
1925	M Y A S P S M W E N L	1330.7	- (SEQ ID NO: 1541)
1927	M Y A S P S F P E N L	1257.5	- (SEQ ID NO: 1542)
1928	M Y A S P S F F E N L	1307.5	- (SEQ ID NO: 1543)
1929	M Y A S P S F Y E N L	1323.5	- (SEQ ID NO: 1544)
1930	M Y A S P S F W E N L	1346.6	- (SEQ ID NO: 1545)
1932	M Y A S P S Y P E N L	1273.5	- (SEQ ID NO: 1546)
[illegible]			

[illegible]	M Y A S P S D P E N L	1225.4	(SEQ ID NO: 1550)

1938	M Y A S P S D F E N L	1275.4	- (SEQ ID NO: 1551)
1939	M Y A S P S D Y E N L	1291.4	- (SEQ ID NO: 1552)
1940	M Y A S P S D W E N L	1314.5	- (SEQ ID NO: 1553)
1942	M Y A S P S E P E N L	1239.4	- (SEQ ID NO: 1554)
1943	M Y A S P S E F E N L	1289.4	- (SEQ ID NO: 1555)
1944	M Y A S P S E Y E N L	1305.4	- (SEQ ID NO: 1556)
1945	M Y A S P S E W E N L	1328.5	- (SEQ ID NO: 1557)
1947	M Y A S P S N P E N L	1224.5	- (SEQ ID NO: 1558)
1948	M Y A S P S N F E N L	1274.5	- (SEQ ID NO: 1559)
1949	M Y A S P S N Y E N L	1290.5	- (SEQ ID NO: 1560)
1950	M Y A S P S N W E N L	1313.6	- (SEQ ID NO: 1561)
1952	M Y A S P S Q P E N L	1238.5	- (SEQ ID NO: 1562)
1953	M Y A S P S Q F E N L	1288.5	- (SEQ ID NO: 1563)
1954	M Y A S P S Q Y E N L	1304.5	- (SEQ ID NO: 1564)
1955	M Y A S P S Q W E N L	1327.6	- (SEQ ID NO: 1565)
1957	M Y A S P S H P E N L	1247.5	- (SEQ ID NO: 1566)
1958	M Y A S P S H F E N L	1297.5	- (SEQ ID NO: 1567)
1959	M Y A S P S H Y E N L	1313.5	- (SEQ ID NO: 1568)
1960	M Y A S P S H W E N L	1336.6	- (SEQ ID NO: 1569)
1962	M F R S P S M P E N L	1310.7	- (SEQ ID NO: 1570)
1963	M F R S P S M F E N L	1360.7	- (SEQ ID NO: 1571)
1964	M F R S P S M Y E N L	1376.7	- (SEQ ID NO: 1572)
1965	M F R S P S M W E N L	1399.8	- (SEQ ID NO: 1573)
1967	M F R S P S F P E N L	1326.6	- (SEQ ID NO: 1574)
1968	M F R S P S F F E N L	1376.6	- (SEQ ID NO: 1575)
1969	M F R S P S F Y E N L	1392.6	- (SEQ ID NO: 1576)
1970	M F R S P S F W E N L	1415.7	- (SEQ ID NO: 1577)
1972	M F R S P S Y P E N L	1342.6	- (SEQ ID NO: 1578)
1973	M F R S P S Y F E N L	1392.6	- (SEQ ID NO: 1579)
1974	M F R S P S Y Y E N L	1408.6	- (SEQ ID NO: 1580)
1975	M F R S P S Y W E N L	1431.7	- (SEQ ID NO: 1581)
1977	M F R S P S D P E N L	1294.5	- (SEQ ID NO: 1582)
1978	M F R S P S D F E N L	1344.5	- (SEQ ID NO: 1583)
[illegible]			

1983	M F R S P S E F E N L	1359.5	(SEQ ID NO: 1587)

1984 M F R S P S E Y E N L 1374.5	-	(SEQ ID NO: 1588)
1985 M F R S P S E W E N L 1397.6	-	(SEQ ID NO: 1589)
1987 M F R S P S N P E N L 1293.6	-	(SEQ ID NO: 1590)
1988 M F R S P S N F E N L 1343.6	-	(SEQ ID NO: 1591)
1989 M F R S P S N Y E N L 1359.6	-	(SEQ ID NO: 1592)
1990 M F R S P S N W E N L 1382.7	-	(SEQ ID NO: 1593)
1992 M F R S P S Q P E N L 1307.6	-	(SEQ ID NO: 1594)
1993 M F R S P S Q F E N L 1357.6	-	(SEQ ID NO: 1595)
1994 M F R S P S Q Y E N L 1373.6	-	(SEQ ID NO: 1596)
1995 M F R S P S Q W E N L 1396.7	-	(SEQ ID NO: 1597)
1997 M F R S P S H P E N L 1316.6	-	(SEQ ID NO: 1598)
1998 M F R S P S H F E N L 1366.6	-	(SEQ ID NO: 1599)
1999 M F R S P S H Y E N L 1382.6	-	(SEQ ID NO: 1600)
2000 M F R S P S H W E N L 1405.7	-	(SEQ ID NO: 1601)
2002 M F S S P S M P E N L 1242.4	-	(SEQ ID NO: 1602)
2003 M F S S P S M F E N L 1292.4	-	(SEQ ID NO: 1603)
2004 M F S S P S M Y E N L 1308.4	-	(SEQ ID NO: 1604)
2005 M F S S P S M W E N L 1331.5	-	(SEQ ID NO: 1605)
2007 M F S S P S F P E N L 1258.3	-	(SEQ ID NO: 1606)
2008 M F S S P S F F E N L 1308.3	-	(SEQ ID NO: 1607)
2009 M F S S P S F Y E N L 1324.3	-	(SEQ ID NO: 1608)
2010 M F S S P S F W E N L 1347.4	-	(SEQ ID NO: 1609)
2012 M F S S P S Y P E N L 1274.3	-	(SEQ ID NO: 1610)
2013 M F S S P S Y F E N L 1324.3	-	(SEQ ID NO: 1611)
2014 M F S S P S Y Y E N L 1340.3	-	(SEQ ID NO: 1612)
2015 M F S S P S Y W E N L 1363.4	-	(SEQ ID NO: 1613)
2017 M F S S P S D P E N L 1226.2	-	(SEQ ID NO: 1614)
2018 M F S S P S D F E N L 1276.2	-	(SEQ ID NO: 1615)
2019 M F S S P S D Y E N L 1292.2	-	(SEQ ID NO: 1616)
2020 M F S S P S D W E N L 1315.3	-	(SEQ ID NO: 1617)
2022 M F S S P S E P E N L 1240.2	-	(SEQ ID NO: 1618)
2023 M F S S P S E F E N L 1290.2	-	(SEQ ID NO: 1619)
2024 M F S S P S E Y E N L 1306.2	-	(SEQ ID NO: 1620)
[illegible]	[illegible]	[illegible]

2029 M F S S P S N Y E N L 1291.3 (SEQ ID NO: 1624)

2030 M F S S P S N W E N L 1314.4 - (SEQ ID NO: 1625)

2032 M F S S P S Q P E N L 1239.3 - (SEQ ID NO: 1626)

2033 M F S S P S Q F E N L 1289.3 - (SEQ ID NO: 1627)

2034 M F S S P S Q Y E N L 1305.3 - (SEQ ID NO: 1628)

2035 M F S S P S Q W E N L 1328.4 - (SEQ ID NO: 1629)

2037 M F S S P S H P E N L 1248.3 - (SEQ ID NO: 1630)

2038 M F S S P S H F E N L 1298.3 - (SEQ ID NO: 1631)

2039 M F S S P S H Y E N L 1314.3 - (SEQ ID NO: 1632)

2040 M F S S P S H W E N L 1337.4 - (SEQ ID NO: 1633)

2042 M F T S P S M P E N L 1255.6 - (SEQ ID NO: 1634)

2043 M F T S P S M F E N L 1305.6 - (SEQ ID NO: 1635)

2044 M F T S P S M Y E N L 1321.6 - (SEQ ID NO: 1636)

2045 M F T S P S M W E N L 1344.7 - (SEQ ID NO: 1637)

2047 M F T S P S F P E N L 1271.5 - (SEQ ID NO: 1638)

2048 M F T S P S F F E N L 1321.5 - (SEQ ID NO: 1639)

2049 M F T S P S F Y E N L 1337.5 - (SEQ ID NO: 1640)

2050 M F T S P S F W E N L 1360.6 - (SEQ ID NO: 1641)

2052 M F T S P S Y P E N L 1287.5 - (SEQ ID NO: 1642)

2053 M F T S P S Y F E N L 1337.5 - (SEQ ID NO: 1643)

2054 M F T S P S Y Y E N L 1353.5 - (SEQ ID NO: 1644)

2055 M F T S P S Y W E N L 1376.6 - (SEQ ID NO: 1645)

2057 M F T S P S D P E N L 1239.4 - (SEQ ID NO: 1646)

2058 M F T S P S D F E N L 1289.4 - (SEQ ID NO: 1647)

2059 M F T S P S D Y E N L 1305.4 - (SEQ ID NO: 1648)

2060 M F T S P S D W E N L 1328.5 - (SEQ ID NO: 1649)

2062 M F T S P S E P E N L 1253.4 - (SEQ ID NO: 1650)

2063 M F T S P S E F E N L 1303.4 - (SEQ ID NO: 1651)

2064 M F T S P S E Y E N L 1319.4 - (SEQ ID NO: 1652)

2065 M F T S P S E W E N L 1342.5 - (SEQ ID NO: 1653)

2067 M F T S P S N P E N L 1238.5 - (SEQ ID NO: 1654)

2068 M F T S P S N F E N L 1288.5 - (SEQ ID NO: 1655)

2069 M F T S P S N Y E N L 1304.5 - (SEQ ID NO: 1656)

2070 M F T S P S N W E N L 1327.6 - (SEQ ID NO: 1657)

2075 M F T S P S Q W E N L 1341.6 - (SEQ ID NO: 1661)

2077	M F T S P S H P E N L	1261.5	- (SEQ ID NO: 1662)
2078	M F T S P S H F E N L	1311.5	- (SEQ ID NO: 1663)
2079	M F T S P S H Y E N L	1327.5	- (SEQ ID NO: 1664)
2080	M F T S P S H W E N L	1350.6	- (SEQ ID NO: 1665)
2082	M F H S P S M P E N L	1291.7	- (SEQ ID NO: 1666)
2083	M F H S P S M F E N L	1341.7	- (SEQ ID NO: 1667)
2084	M F H S P S M Y E N L	1357.7	- (SEQ ID NO: 1668)
2085	M F H S P S M W E N L	1380.8	- (SEQ ID NO: 1669)
2087	M F H S P S F P E N L	1307.6	- (SEQ ID NO: 1670)
2088	M F H S P S F F E N L	1357.6	- (SEQ ID NO: 1671)
2089	M F H S P S F Y E N L	1373.6	- (SEQ ID NO: 1672)
2090	M F H S P S F W E N L	1396.7	- (SEQ ID NO: 1673)
2092	M F H S P S Y P E N L	1323.6	- (SEQ ID NO: 1674)
2093	M F H S P S Y F E N L	1373.6	- (SEQ ID NO: 1675)
2094	M F H S P S Y Y E N L	1389.6	- (SEQ ID NO: 1676)
2095	M F H S P S Y W E N L	1412.7	- (SEQ ID NO: 1677)
2097	M F H S P S D P E N L	1275.5	- (SEQ ID NO: 1678)
2098	M F H S P S D F E N L	1325.5	- (SEQ ID NO: 1679)
2099	M F H S P S D Y E N L	1341.5	- (SEQ ID NO: 1680)
2100	M F H S P S D W E N L	1364.6	- (SEQ ID NO: 1681)
2102	M F H S P S E P E N L	1289.5	- (SEQ ID NO: 1682)
2103	M F H S P S E F E N L	1339.5	- (SEQ ID NO: 1683)
2104	M F H S P S E Y E N L	1355.5	- (SEQ ID NO: 1684)
2105	M F H S P S E W E N L	1378.6	- (SEQ ID NO: 1685)
2107	M F H S P S N P E N L	1274.6	- (SEQ ID NO: 1686)
2108	M F H S P S N F E N L	1324.6	- (SEQ ID NO: 1687)
2109	M F H S P S N Y E N L	1340.6	- (SEQ ID NO: 1688)
2110	M F H S P S N W E N L	1363.7	- (SEQ ID NO: 1689)
2112	M F H S P S Q P E N L	1288.6	- (SEQ ID NO: 1690)
2113	M F H S P S Q F E N L	1338.6	- (SEQ ID NO: 1691)
2114	M F H S P S Q Y E N L	1354.6	- (SEQ ID NO: 1692)
2115	M F H S P S Q W E N L	1377.7	- (SEQ ID NO: 1693)
2117	M F H S P S H P E N L	1297.6	- (SEQ ID NO: 1694)
[illegible]			
2122	M F N S P S M P E N L	1268	(SEQ ID NO: 1698)

2123 M F N S P S M F E N L 1318.7	-	(SEQ ID NO: 1699)
2124 M F N S P S M Y E N L 1334.7	-	(SEQ ID NO: 1700)
2125 M F N S P S M W E N L 1357.8	-	(SEQ ID NO: 1701)
2127 M F N S P S F P E N L 1284.6	-	(SEQ ID NO: 1702)
2128 M F N S P S F F E N L 1334.6	-	(SEQ ID NO: 1703)
2129 M F N S P S F Y E N L 1350.6	-	(SEQ ID NO: 1704)
2130 M F N S P S F W E N L 1373.7	-	(SEQ ID NO: 1705)
2132 M F N S P S Y P E N L 1300.6	-	(SEQ ID NO: 1706)
2133 M F N S P S Y F E N L 1350.6	-	(SEQ ID NO: 1707)
2134 M F N S P S Y Y E N L 1366.6	-	(SEQ ID NO: 1708)
2135 M F N S P S Y W E N L 1389.7	-	(SEQ ID NO: 1709)
2137 M F N S P S D P E N L 1252.5	-	(SEQ ID NO: 1710)
2138 M F N S P S D F E N L 1302.5	-	(SEQ ID NO: 1711)
2139 M F N S P S D Y E N L 1318.5	-	(SEQ ID NO: 1712)
2140 M F N S P S D W E N L 1341.6	-	(SEQ ID NO: 1713)
2142 M F N S P S E P E N L 1266.5	-	(SEQ ID NO: 1714)
2143 M F N S P S E F E N L 1316.5	-	(SEQ ID NO: 1715)
2144 M F N S P S E Y E N L 1332.5	-	(SEQ ID NO: 1716)
2145 M F N S P S E W E N L 1355.6	-	(SEQ ID NO: 1717)
2147 M F N S P S N P E N L 1251.6	-	(SEQ ID NO: 1718)
2148 M F N S P S N F E N L 1301.6	-	(SEQ ID NO: 1719)
2149 M F N S P S N Y E N L 1317.6	-	(SEQ ID NO: 1720)
2150 M F N S P S N W E N L 1340.7	-	(SEQ ID NO: 1721)
2152 M F N S P S Q P E N L 1265.6	-	(SEQ ID NO: 1722)
2153 M F N S P S Q F E N L 1315.6	-	(SEQ ID NO: 1723)
2154 M F N S P S Q Y E N L 1331.6	-	(SEQ ID NO: 1724)
2155 M F N S P S Q W E N L 1354.7	-	(SEQ ID NO: 1725)
2157 M F N S P S H P E N L 1274.6	-	(SEQ ID NO: 1726)
2158 M F N S P S H F E N L 1324.6	-	(SEQ ID NO: 1727)
2159 M F N S P S H Y E N L 1340.6	-	(SEQ ID NO: 1728)
2160 M F N S P S H W E N L 1363.7	-	(SEQ ID NO: 1729)
2162 M F G S P S M P E N L 1211.6	-	(SEQ ID NO: 1730)
2163 M F G S P S M F E N L 1261.6	-	(SEQ ID NO: 1731)
[illegible]	[illegible]	[illegible]
2168 M F G S P S F F E N L [illegible]	[illegible]	(SEQ ID NO: 1735)

2169	M F G S P S F Y E N L	1293.5	- (SEQ ID NO: 1736)
2170	M F G S P S F W E N L	1316.6	- (SEQ ID NO: 1737)
2172	M F G S P S Y P E N L	1243.5	- (SEQ ID NO: 1738)
2173	M F G S P S Y F E N L	1293.5	- (SEQ ID NO: 1739)
2174	M F G S P S Y Y E N L	1309.5	- (SEQ ID NO: 1740)
2175	M F G S P S Y W E N L	1332.6	- (SEQ ID NO: 1741)
2177	M F G S P S D P E N L	1195.4	- (SEQ ID NO: 1742)
2178	M F G S P S D F E N L	1245.4	- (SEQ ID NO: 1743)
2179	M F G S P S D Y E N L	1261.4	- (SEQ ID NO: 1744)
2180	M F G S P S D W E N L	1284.5	- (SEQ ID NO: 1745)
2182	M F G S P S E P E N L	1209.4	- (SEQ ID NO: 1746)
2183	M F G S P S E F E N L	1259.4	- (SEQ ID NO: 1747)
2184	M F G S P S E Y E N L	1275.4	- (SEQ ID NO: 1748)
2185	M F G S P S E W E N L	1298.5	- (SEQ ID NO: 1749)
2187	M F G S P S N P E N L	1194.5	- (SEQ ID NO: 1750)
2188	M F G S P S N F E N L	1244.5	- (SEQ ID NO: 1751)
2189	M F G S P S N Y E N L	1260.5	- (SEQ ID NO: 1752)
2190	M F G S P S N W E N L	1283.6	- (SEQ ID NO: 1753)
2192	M F G S P S Q P E N L	1208.5	- (SEQ ID NO: 1754)
2193	M F G S P S Q F E N L	1258.5	- (SEQ ID NO: 1755)
2194	M F G S P S Q Y E N L	1274.5	- (SEQ ID NO: 1756)
2195	M F G S P S Q W E N L	1297.6	- (SEQ ID NO: 1757)
2197	M F G S P S H P E N L	1217.5	- (SEQ ID NO: 1758)
2198	M F G S P S H F E N L	1267.5	- (SEQ ID NO: 1759)
2199	M F G S P S H Y E N L	1283.5	- (SEQ ID NO: 1760)
2200	M F G S P S H W E N L	1306.6	- (SEQ ID NO: 1761)
2202	M F A S P S M P E N L	1225.6	- (SEQ ID NO: 1762)
2203	M F A S P S M F E N L	1275.6	- (SEQ ID NO: 1763)
2204	M F A S P S M Y E N L	1291.6	- (SEQ ID NO: 1764)
2205	M F A S P S M W E N L	1314.7	- (SEQ ID NO: 1765)
2207	M F A S P S F P E N L	1241.5	- (SEQ ID NO: 1766)
2208	M F A S P S F F E N L	1291.5	- (SEQ ID NO: 1767)
2209	M F A S P S F Y E N L	1307.5	- (SEQ ID NO: 1768)
[illegible]			
2214	M F A S P S Y Y E N L	1323.5	(SEQ ID NO: 1772)

2215 M F A S P S Y W E N L 1346.6	-	(SEQ ID NO: 1773)
2217 M F A S P S D P E N L 1209.4	-	(SEQ ID NO: 1774)
2218 M F A S P S D F E N L 1259.4	-	(SEQ ID NO: 1775)
2219 M F A S P S D Y E N L 1275.4	-	(SEQ ID NO: 1776)
2220 M F A S P S D W E N L 1298.5	-	(SEQ ID NO: 1777)
2222 M F A S P S E P E N L 1223.4	-	(SEQ ID NO: 1778)
2223 M F A S P S E F E N L 1273.4	-	(SEQ ID NO: 1779)
2224 M F A S P S E Y E N L 1289.4	-	(SEQ ID NO: 1780)
2225 M F A S P S E W E N L 1312.5	-	(SEQ ID NO: 1781)
2227 M F A S P S N P E N L 1208.5	-	(SEQ ID NO: 1782)
2228 M F A S P S N F E N L 1258.5	-	(SEQ ID NO: 1783)
2229 M F A S P S N Y E N L 1274.5	-	(SEQ ID NO: 1784)
2230 M F A S P S N W E N L 1297.6	-	(SEQ ID NO: 1785)
2232 M F A S P S Q P E N L 1222.5	-	(SEQ ID NO: 1786)
2233 M F A S P S Q F E N L 1272.5	-	(SEQ ID NO: 1787)
2234 M F A S P S Q Y E N L 1288.5	-	(SEQ ID NO: 1788)
2235 M F A S P S Q W E N L 1311.6	-	(SEQ ID NO: 1789)
2237 M F A S P S H P E N L 1231.5	-	(SEQ ID NO: 1790)
2238 M F A S P S H F E N L 1281.5	-	(SEQ ID NO: 1791)
2239 M F A S P S H Y E N L 1297.5	-	(SEQ ID NO: 1792)
2240 M F A S P S H W E N L 1320.6	-	(SEQ ID NO: 1793)
2242 R Y S L P P E L S N M 1308.6	-	(SEQ ID NO: 1794)
2243 A Y R S P S M P E N L 1266.5	-	(SEQ ID NO: 1795)
2244 R Y R S P S M P E N L 1351.6	-	(SEQ ID NO: 1796)
2245 N Y R S P S M P E N L 1309.6	-	(SEQ ID NO: 1797)
2246 D Y R S P S M P E N L 1310.5	-	(SEQ ID NO: 1798)
2247 C Y R S P S M P E N L 1298.6	-	(SEQ ID NO: 1799)
2248 Q Y R S P S M P E N L 1323.6	-	(SEQ ID NO: 1800)
2249 E Y R S P S M P E N L 1324.5	-	(SEQ ID NO: 1801)
2250 G Y R S P S M P E N L 1252.5	-	(SEQ ID NO: 1802)
2251 H Y R S P S M P E N L 1332.6	-	(SEQ ID NO: 1803)
2252 I Y R S P S M P E N L 1308.6	-	(SEQ ID NO: 1804)
2253 L Y R S P S M P E N L 1308.6	-	(SEQ ID NO: 1805)
2254 K Y R S P S M P E N L 1323.6		

2257 P Y R S P S M P E N L 1292.6 (SEQ ID NO: 1809)

2258	S Y R S P S M P E N L	1283.3	- (SEQ ID NO: 1810)
2259	T Y R S P S M P E N L	1296.5	- (SEQ ID NO: 1811)
2260	W Y R S P S M P E N L	1381.7	- (SEQ ID NO: 1812)
2261	Y Y R S P S M P E N L	1358.6	- (SEQ ID NO: 1813)
2262	V Y R S P S M P E N L	1294.6	- (SEQ ID NO: 1814)
2263	L A R S P S M P E N L	1216.5	- (SEQ ID NO: 1815)
2264	L R R S P S M P E N L	1301.6	- (SEQ ID NO: 1816)
2265	L N R S P S M P E N L	1259.6	- (SEQ ID NO: 1817)
2266	L D R S P S M P E N L	1260.5	- (SEQ ID NO: 1818)
2267	L C R S P S M P E N L	1248.6	- (SEQ ID NO: 1819)
2268	L Q R S P S M P E N L	1273.6	- (SEQ ID NO: 1820)
2269	L E R S P S M P E N L	1274.5	- (SEQ ID NO: 1821)
2270	L G R S P S M P E N L	1202.5	- (SEQ ID NO: 1822)
2271	L H R S P S M P E N L	1282.6	- (SEQ ID NO: 1823)
2272	L I R S P S M P E N L	1258.6	- (SEQ ID NO: 1824)
2273	L L R S P S M P E N L	1258.6	- (SEQ ID NO: 1825)
2274	**L K R S P S M P E N L**	**1273.6**	- (SEQ ID NO: 1826)
2275	L M R S P S M P E N L	1276.7	- (SEQ ID NO: 1827)
2276	L F R S P S M P E N L	1292.6	- (SEQ ID NO: 1828)
2277	L P R S P S M P E N L	1242.6	- (SEQ ID NO: 1829)
2278	L S R S P S M P E N L	1233.3	- (SEQ ID NO: 1830)
2279	L T R S P S M P E N L	1246.5	- (SEQ ID NO: 1831)
2280	L W R S P S M P E N L	1331.7	- (SEQ ID NO: 1832)
2281	L Y R S P S M P E N L	1308.6	- (SEQ ID NO: 1833)
2282	L V R S P S M P E N L	1244.6	- (SEQ ID NO: 1834)
2283	L Y A S P S M P E N L	1223.5	- (SEQ ID NO: 1835)
2284	L Y R S P S M P E N L	1308.6	- (SEQ ID NO: 1836)
2285	L Y N S P S M P E N L	1266.6	- (SEQ ID NO: 1837)
2286	L Y D S P S M P E N L	1267.5	- (SEQ ID NO: 1838)
2287	L Y C S P S M P E N L	1255.6	- (SEQ ID NO: 1839)
2288	L Y Q S P S M P E N L	1280.6	- (SEQ ID NO: 1840)
2289	L Y E S P S M P E N L	1281.5	- (SEQ ID NO: 1841)
2290	L Y G S P S M P E N L	1209.5	- (SEQ ID NO: 1842)

2294	L Y K S P S M P E N L	1280.6	(SEQ ID NO: 1846)

2295	L Y M S P S M P E N L	1283.7	- (SEQ ID NO: 1847)
2296	L Y F S P S M P E N L	1299.6	- (SEQ ID NO: 1848)
2297	L Y P S P S M P E N L	1249.6	- (SEQ ID NO: 1849)
2298	L Y S S P S M P E N L	1240.3	- (SEQ ID NO: 1850)
2299	L Y T S P S M P E N L	1253.5	- (SEQ ID NO: 1851)
2300	L Y W S P S M P E N L	1338.7	- (SEQ ID NO: 1852)
2301	L Y Y S P S M P E N L	1315.6	- (SEQ ID NO: 1853)
2302	L Y V S P S M P E N L	1251.6	- (SEQ ID NO: 1854)
2303	L Y R S P S A P E N L	1248.4	- (SEQ ID NO: 1855)
2304	L Y R S P S R P E N L	1333.5	- (SEQ ID NO: 1856)
2305	L Y R S P S N P E N L	1291.5	- (SEQ ID NO: 1857)
2306	L Y R S P S D P E N L	1292.4	- (SEQ ID NO: 1858)
2307	L Y R S P S C P E N L	1280.5	- (SEQ ID NO: 1859)
2308	L Y R S P S Q P E N L	1305.5	- (SEQ ID NO: 1860)
2309	L Y R S P S E P E N L	1306.4	- (SEQ ID NO: 1861)
2310	L Y R S P S G P E N L	1234.4	- (SEQ ID NO: 1862)
2311	L Y R S P S H P E N L	1314.5	- (SEQ ID NO: 1863)
2312	L Y R S P S I P E N L	1290.5	- (SEQ ID NO: 1864)
2313	L Y R S P S L P E N L	1290.5	- (SEQ ID NO: 1865)
2314	L Y R S P S K P E N L	1305.5	- (SEQ ID NO: 1866)
2315	L Y R S P S M P E N L	1308.6	- (SEQ ID NO: 1867)
2316	L Y R S P S F P E N L	1324.5	- (SEQ ID NO: 1868)
2317	L Y R S P S P P E N L	1274.5	- (SEQ ID NO: 1869)
2318	L Y R S P S S P E N L	1265.2	- (SEQ ID NO: 1870)
2319	L Y R S P S T P E N L	1278.4	- (SEQ ID NO: 1871)
2320	L Y R S P S W P E N L	1363.6	- (SEQ ID NO: 1872)
2321	L Y R S P S Y P E N L	1340.5	- (SEQ ID NO: 1873)
2322	L Y R S P S V P E N L	1276.5	- (SEQ ID NO: 1874)
2323	L Y R S P S M A E N L	1282.5	- (SEQ ID NO: 1875)
2324	L Y R S P S M R E N L	1367.6	- (SEQ ID NO: 1876)
2325	L Y R S P S M N E N L	1325.6	- (SEQ ID NO: 1877)
2326	L Y R S P S M D E N L	1326.5	- (SEQ ID NO: 1878)
2327	L Y R S P S M C E N L	1314.6	- (SEQ ID NO: 1879)

2331	L Y R S P S M H E N L	1348.6	(SEQ ID NO: 1883)

2332	L Y R S P S M I E N L	1324.6	- (SEQ ID NO: 1884)
2333	L Y R S P S M L E N L	1324.6	- (SEQ ID NO: 1885)
2334	L Y R S P S M K E N L	1339.6	- (SEQ ID NO: 1886)
2335	L Y R S P S M M E N L	1342.7	- (SEQ ID NO: 1887)
2336	L Y R S P S M F E N L	1358.6	- (SEQ ID NO: 1888)
2337	L Y R S P S M P E N L	1308.6	- (SEQ ID NO: 1889)
2338	L Y R S P S M S E N L	1299.3	- (SEQ ID NO: 1890)
2339	L Y R S P S M T E N L	1312.5	- (SEQ ID NO: 1891)
2340	L Y R S P S M W E N L	1397.7	- (SEQ ID NO: 1892)
2341	L Y R S P S M Y E N L	1374.6	- (SEQ ID NO: 1893)
2342	L Y R S P S M V E N L	1310.6	- (SEQ ID NO: 1894)

Example 3: G2 abrogating peptides of the invention

The following example describes studies which identified exemplary G2 checkpoint-abrogating peptides of the invention. The following peptides of the invention were synthesized directly on membranes and tested in *in vitro* phosphorylation ("kination" assays, as described above.

Table 2 (SEQ ID NOS 1922-1929)

PEPTIDE	X_1	X_2	X_3	X_4	X_5	X_6	X_7	X_8	X_9	X_{10}	X_{11}
AAA	L	A	R	S	A	S	M	P	E	A	L
RANDOMII	R	Y	S	L	P	P	E	L	S	N	M
S216A	L	Y	R	S	P	A	M	P	E	N	L
S216P	L	Y	R	S	P	S	M	P	E	N	L
YPN		Y	G	G	P	G	G	G	G	N	
YG7N		Y	G	G	G	G	G	G	G	N	
YG6N		Y	G	G	G	G	G	G		N	
YG5N		Y	G	G	G	G	G			N	
YPN		Y			P					N	
RPI			R					P			I

These peptides were tested in *in vitro* kination reactions. The oligopeptides were used as phosphorylation substrates; added kinases are involved in the cell cycle G2 checkpoint. Thus, a substance that inhibits the kination reaction can be a cell cycle G2 checkpoint abrogator. For the detection of the phosphorylation status of substrates in this screening method, isotope-labeled ATP and anti-phospho-peptides antibody can be used.

hChk1; hChk1 fusion proteins (MBP-peptide, GST-peptide), HuCds1/Chk2; HuCds1/Chk2 fusion proteins (MBP-peptide, GST-peptide); or, the cell extract from DNA damaged cells, can be used as the kinases in the screening assay.

The oligopeptides tested as substrates are Y X_2 X_3 P S X_6 X_7 X_8 N (SEQ ID NO: 1930) (X_3 through X_6, respectively; the first position (X_1) "Y" in this abbreviated nine residue motif corresponds to position X_2 in the eleven residue motif, described above) and variations thereof wherein amino acid residues at positions 2 (X_2) and position 3 (X_3) are Gly, Leu, Ser, or Arg; and the amino acid residue at position 6 through 8 are Gly, Leu, Ser, Met, Pro or Glu. Other tested oligopeptides sequence variations have amino acid residues at position 2 as Gly, Leu, Ser, or Arg; amino acid residues at position 3 as Gly, Leu or Ser; amino acid residues at position 6 as Gly, Met, Pro or Glu; amino acid residues at position 7 as Gly, Leu, or Pro; and, amino acid residues at position 8 as Gly, Met, Ser or Glu. In another variation the residue at position 2 was Arg; position 3 was Ser; position 6 was Met; position 7 was Pro; and, position 8 was Glu.

The cells with the deficient cell cycle G1 checkpoint (such as a human leukemia-derived cell line Jurkat) were treated with a DNA damaging treatment. As the DNA damaging treatment, the cells were treated with bleomycin or other anti-cancer drugs. These drugs were added to the cell culture medium. Alternatively, the cells were irradiated with gamma irradiation. Peptides were added to these cells and the amount of DNA was determined some 10 to 48 hours after the DNA damage. The harvested cells were re-suspended with the solution that includes propidium iodide, RNase and NP-40 and analyzed by flow cytometer. If the oligopeptide "candidate substance" induces cells not to accumulate DNA at G2/M by this analysis, the result is positive and the substance potentially abrogated cell cycle checkpoint. For, the cells are simultaneously treated with an oligopeptide

"candidate phosphorylation substrate" and an M phase checkpoint activator, such as colchicine or nocodazol. The DNA content of the cells are analyzed some 10 to 48 hours after the treatment as described above. The candidates that do not disturb the accumulation of the cells at G2/M will be the selected G2 checkpoint abrogators in this screening method.

In one embodiment, G2 checkpoint abrogators at positions 2 and 3 the have amino acid residues Gly, Leu, Ser or Arg, and at position 5 to 8 are amino acid residues Ser, Gly, Met, Pro or Glu.

In one embodiment of the invention the compositions are enhancers or augmenters of a DNA damaging anti-cancer treatment. By treating cancer cells simultaneously or sequentially with an anti-cancer treatment and a G2 checkpoint inhibiting composition of the invention, one can effectively kill the cancer cells. Since the most human cancer cells do not have an intact G1 checkpoint, the abrogation of the G2 checkpoint by a G2 checkpoint inhibiting composition of the invention will effectively kill the cancer cells that are treated with a DNA damaging method. The compositions of the invention can be directly used as a drug (e.g., a pharmaceutical compositions) or these oligopeptides could be expressed recombinantly *in vivo*, e.g., from a virus vector or other expression vector, e.g., a plasmid, as an *in vivo* gene therapy.

Jurkat cells were cultured in 10% fetal calf serum with a medium (RPMI 1640) at 37°C/5% CO_2 with: bleomycin at 20 μg/ml; bleomycin at 20 μg/ml and the peptide "4aa" (amino acid sequence is GGSPSM (SEQ ID NO: 1931)); bleomycin at 20 μg/ml and the peptide AAA (Table 1); bleomycin at 20 μg/ml and the peptide YNP (Table 1). The amount of DNA was analyzed at 0, 6, 12, 24 hours after the addition of ten microgram of bleomycin with or without the oligopeptides "4aa," "YNP" and "AAA." The DNA quantity was analyzed by a flow cytometer (FACS) after the addition of a solution comprising propidium iodide, RNase and NP-40.

The results are shown in Figure 6. The left panels are actual results of flow cytometer (FACS) analysis. The right panel indicates the population of cells in each of the cell cycle phases (sub G1, G1, S, and G2 M). The results indicated that YNP peptide

instead of bleomycin; colchicine at 2.5 μg ml; colchicine at 2.5 μg ml and the peptide "4aa".

colchicine at 2.5 μg/ml and the peptide AAA (Table 1); colchicine at 2.5 μg/ml and the peptide YNP (Table 1), and no treatment. The results are shown in Figure 7. None of the above tested oligopeptides (Table 1), including, YPN, affected the accumulation of the colchicine-treated cells at the G2/M phase. These data indicated that YPN specifically abrogated the cell cycle at the G2 checkpoint.

Peptides which were tested and the results of these experiments are further summarized in Figures 8 and 9.

Example 4: Peptides of the invention sensitize cancer cells in *in vivo* animal model

The following example describes studies in an art-accepted animal model which demonstrated that exemplary peptides of the invention are effective agents for selectively sensitizing cancer cells to DNA damaging agents. In particular, nude mouse studies demonstrated the *in vivo* efficacy of the compositions and methods of the invention.

Human colon cancer cell line SW620 were injected subcutaneously into 3 week old Balb/c nude mouse ($1x10^6$ cells per mouse). Some two weeks after the injection, the established subcutaneous tumors of diameter 2 to 4 mm were resected and transplanted to syngeneic mice. One week after the transplantation, the injection of cisplatin (CDDP) and peptides (TAT-control and TAT-S216, see Table 1) was started. The peptides were in the form of recombinant fusion proteins, with TAT being the protein transduction domain having the sequence YGRKKRRQRRR (SEQ ID NO: 1899).

Cisplatin (CDDP) at 6 mg/kg was injected once a week into peritoneum. Peptides (at 100 nM) were injected into tumor twice a week. Relative tumor weights were assessed at 3 and 5 weeks. The results are shown in Figure 10, upper panel. Similar experiments were performed with 5-FU instead of cisplatin. The results are shown in Figure 8, lower panel. As shown in Figure 10, the S216-containing fusion protein effectively sensitized the cancer cells to a DNA damaging agent administered to the animal *in vivo*.

Similar experiments were performed with cisplatin (CDDP) and another exemplary peptide of the invention, "random II" or "R-II" (see Table 1). As with S216, RII peptide was in the form of a recombinant fusion protein with TAT. The [illegible]

shown in Figure 11, the R-II containing fusion protein effectively sensitized the cancer cells to a DNA damaging agent administered to the animal *in vivo*.

A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. An isolated or recombinant polypeptide comprising the amino acid sequence:

$X_1\ X_2\ X_3\ X_4\ X_5\ X_6\ X_7\ X_8\ X_9\ X_{10}\ X_{11}$

wherein X1 is L, F, W, M, R, I, V, Y, K, or absent,

X2 is Y, F, A, W, S or T,

X3 is any amino acid,

X4 is any amino acid,

X5 is any amino acid,

X6 is S, A, N, H or P,

X7 is any amino acid,

X8 is any amino acid,

X9 is any amino acid or absent,

X10 is N, G, L, S, M, P, N, A or absent, and

X11 is L or absent,

wherein the polypeptide when administered to or expressed in a cell disrupts the G2 cell cycle arrest checkpoint.

2. The isolated or recombinant polypeptide of claim 1, wherein X_1 is L, F, W, M, R or absent.

3. The isolated or recombinant polypeptide of claim 2, wherein X_1 is L, F or W.

4. The isolated or recombinant polypeptide of claim 1, wherein X_2 is Y, F, A

is R, I, S, H, D, G, A, L, K, A, N, Q or P.

6. The isolated or recombinant polypeptide of claim 5, wherein X_3 is R, T, S, H, D, G, A or L.

7. The isolated or recombinant polypeptide of claim 6, wherein X_3 is R, T, S or H.

8. The isolated or recombinant polypeptide of claim 1, wherein X_4 is S, T, G, A, L, R, I, M, V, P.

9. The isolated or recombinant polypeptide of claim 8, wherein X_4 is S, T, G, A, L, R .

10. The isolated or recombinant polypeptide of claim 9, wherein X_4 is S.

11. The isolated or recombinant polypeptide of claim 1, wherein X_5 is P, A, G, S or T.

12. The isolated or recombinant polypeptide of claim 1, wherein X_5 is P.

13. The isolated or recombinant polypeptide of claim 1, wherein X_6 is S, N, H, P, A, G or T.

14. The isolated or recombinant polypeptide of claim 13, wherein X_6 is S, N or H.

16. The isolated or recombinant polypeptide of claim 1, wherein X_7 is M, F, Y, D, E, N, Q, H, G, I, L, V, A, P, N or W.

17. The isolated or recombinant polypeptide of claim 16, wherein X_7 is M, F, Y, D, E, N, Q or H.

18. The isolated or recombinant polypeptide of claim 17, wherein X_7 is M, F, Y, Q or H.

19. The isolated or recombinant polypeptide of claim 1, wherein X_8 is P, F, Y, W, L, G, M, D, E, N, Q, H, I, V, A or P.

20. The isolated or recombinant polypeptide of claim 19, wherein X_8 is P, F, Y or W.

21. The isolated or recombinant polypeptide of claim 20, wherein X_8 is Y.

22. The isolated or recombinant polypeptide of claim 1, wherein X_9 is E, G, L, S, M, P, N, D, A, T, P or absent.

23. The isolated or recombinant polypeptide of claim 1, wherein X_{10} is absent.

24. The isolated or recombinant polypeptide of claim 1, wherein X_{11} is absent.

25. The isolated or recombinant polypeptide of claim 1, wherein X_5 is Y.

26. The isolated or recombinant polypeptide of claim 1, wherein X_3 is R, X_8 is P, and X_{11} is L.

27. The isolated or recombinant polypeptide of claim 1, wherein X_4 is S, X_5 is P, X_6 is S, X_9 is E, X_{10} is N and X_{11} is L.

28. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises Y G G P G G G G N (SEQ ID NO: 1895).

29. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises R Y S L P P E L S N M (SEQ ID NO: 1).

30. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises L A R S A S M P E A L (SEQ ID NO: 1896).

31. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises L Y R S P S M P E N L(SEQ ID NO: 2).

32. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises L Y R S P A M P E N L (SEQ ID NO: 1897).

33. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises W Y R S P S F Y E N L (SEQ ID NO: 904).

34. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises W Y R S P S Y Y E N L (SEQ ID NO: 908).

35. The isolated or recombinant polypeptide of claim 1, wherein the amino

36. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises L Y R S P S Y P E N L (SEQ ID NO: 10), L Y R S P S Y F E N L (SEQ ID NO: 11), L Y R S P S Y Y E N L (SEQ ID NO: 12), or L Y R S P S Y W E N L (SEQ ID NO: 13).

37. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises L Y R S P S N P E N L (SEQ ID NO: 22), L Y R S P S N F E N L (SEQ ID NO: 23), L Y R S P S N Y E N L (SEQ ID NO: 24), or L Y R S P S N W E N L (SEQ ID NO: 25).

38. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises L Y R S P S H P E N L (SEQ ID NO: 30), L Y R S P S H F E N L (SEQ ID NO: 31), L Y R S P S H Y E N L (SEQ ID NO: 32), L Y R S P S H W E N L (SEQ ID NO: 33), L Y S S P S M P E N L (SEQ ID NO: 34), L Y S S P S M F E N L (SEQ ID NO: 35), L Y S S P S M Y E N L (SEQ ID NO: 36), L Y S S P S M W E N L (SEQ ID NO: 37), L Y S S P S F P E N L (SEQ ID NO: 38), L Y S S P S F P E N L (SEQ ID NO: 38), L Y S S P S F F E N L (SEQ ID NO: 39), L Y S S P S F Y E N L (SEQ ID NO: 40), L Y S S P S F W E N L (SEQ ID NO: 41), L Y S S P S Y P E N L (SEQ ID NO: 42), L Y S S P S Y F E N L (SEQ ID NO: 43), L Y S S P S Y Y E N L (SEQ ID NO: 44), or L Y S S P S Y W E N L (SEQ ID NO: 45) .

39. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises L Y S S P S Q P E N L (SEQ ID NO: 58), L Y S S P S Q W E N L (SEQ ID NO: 61), L Y S S P S H P E N L (SEQ ID NO: 62), L Y S S P S H F E N L (SEQ ID NO: 63), L Y S S P S H Y E N L (SEQ ID NO: 64), L Y S S P S H W E N L (SEQ ID NO: 65), L Y T S P S M P E N L (SEQ ID NO: 66), L Y T S P S M F E N L (SEQ ID NO: 67), L Y T S P S M Y E N L (SEQ ID NO: 68), L Y T S P S M W E N L (SEQ ID NO: 69), L Y T S P S F P E N L (SEQ ID NO: 70), L Y T S P S F F E N L (SEQ ID NO: 71), L Y T S P S F Y E N L (SEQ ID NO: 72), L Y T S P S F W E N L (SEQ ID NO: 73), L Y T S P S Y P E N L (SEQ ID NO: 74), L Y T S P S

40. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises L Y T S P S N P E N L (SEQ ID NO: 86), L Y T S P S N F E N L (SEQ ID NO: 87), L Y T S P S N Y E N L (SEQ ID NO: 88) or L Y T S P S N W E N L (SEQ ID NO: 89).

41. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises L Y T S P S H P E N L (SEQ ID NO: 94), L Y T S P S H F E N L (SEQ ID NO: 95), L Y T S P S H Y E N L (SEQ ID NO: 96) or L Y T S P S H W E N L (SEQ ID NO: 97).

42. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises L Y H S P S Y P E N L (SEQ ID NO: 106), L Y H S P S Y F E N L (SEQ ID NO: 107), L Y H S P S Y Y E N L (SEQ ID NO: 108) or L Y H S P S Y W E N L (SEQ ID NO: 109).

43. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises L F T S P S Y P E N L (SEQ ID NO: 298), L F T S P S Y F E N L (SEQ ID NO: 299), L F T S P S Y Y E N L (SEQ ID NO: 300) or L F T S P S Y W E N L (SEQ ID NO: 301).

44. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises F Y S S P S H P E N L (SEQ ID NO: 510), F Y S S P S H F E N L (SEQ ID NO: 511), F Y S S P S H Y E N L (SEQ ID NO: 512), F Y S S P S H W E N L (SEQ ID NO: 513), F Y T S P S M P E N L (SEQ ID NO: 514), F Y T S P S M F E N L (SEQ ID NO: 515), F Y T S P S M Y E N L (SEQ ID NO: 516), F Y T S P S M W E N L (SEQ ID NO: 517), F Y T S P S F P E N L (SEQ ID NO: 518), F Y T S P S F F E N L (SEQ ID NO: 519), F Y T S P S F Y E N L (SEQ ID NO: 520), F Y T S P S F W E N L (SEQ ID NO: 521), F Y T S P S Y P E N L (SEQ ID NO: 522), F Y T S P S Y F E N L (SEQ ID NO: 523), F Y T S P S Y Y E N L (SEQ ID

45. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises W Y R S P S M P E N L (SEQ ID NO: 898), W Y R S P S M F E N L (SEQ ID NO: 899), W Y R S P S M Y E N L (SEQ ID NO: 900), W Y R S P S M W E N L (SEQ ID NO: 901), W Y R S P S F P E N L (SEQ ID NO: 902), W Y R S P S F F E N L (SEQ ID NO: 903), W Y R S P S F Y E N L (SEQ ID NO: 904), W Y R S P S F W E N L (SEQ ID NO: 905), W Y R S P S Y P E N L (SEQ ID NO: 906), W Y R S P S Y F E N L (SEQ ID NO: 907), W Y R S P S Y Y E N L (SEQ ID NO: 908) or W Y R S P S Y W E N L (SEQ ID NO: 909).

46. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises W Y T S P S M P E N L (SEQ ID NO: 962), W Y T S P S M F E N L (SEQ ID NO: 963), W Y T S P S M Y E N L (SEQ ID NO: 964), W Y T S P S M W E N L (SEQ ID NO: 965), W Y T S P S F P E N L (SEQ ID NO: 966), W Y T S P S F F E N L (SEQ ID NO: 967), W Y T S P S F Y E N L (SEQ ID NO: 968), W Y T S P S F W E N L (SEQ ID NO: 969), W Y T S P S Y P E N L (SEQ ID NO: 970), W Y T S P S Y F E N L (SEQ ID NO: 971), W Y T S P S Y Y E N L (SEQ ID NO: 972) or W Y T S P S Y W E N L (SEQ ID NO: 973).

47. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises W Y T S P S H P E N L (SEQ ID NO: 990), W Y T S P S H F E N L (SEQ ID NO: 991), W Y T S P S H Y E N L (SEQ ID NO: 992) or W Y T S P S H W E N L (SEQ ID NO: 993).

48. The isolated or recombinant polypeptide of claim 1, wherein the amino acid sequence comprises L K R S P S M P E N L (SEQ ID NO: 1826), L Y I S P S M P E N L (SEQ ID NO: 1844) or L Y R S P S M V E N L (SEQ ID NO: 1894).

49. The isolated or recombinant polypeptide of claim 1, wherein the cell is a mammalian cell.

51. The isolated or recombinant polypeptide of claim 1, further comprising a cell membrane permeant.

52. The isolated or recombinant polypeptide of claim 51, wherein the cell membrane permeant comprises a polypeptide.

53. The isolated or recombinant polypeptide of claim 52, wherein the polypeptide comprises a TAT protein transduction domain.

54. The isolated or recombinant polypeptide of claim 53, wherein the TAT protein transduction domain is Y G R K K R R Q R R R (SEQ ID NO: 1899).

55. The isolated or recombinant polypeptide of claim 51, wherein the cell membrane permeant comprises a lipid.

56. The isolated or recombinant polypeptide of claim 55, wherein the cell membrane permeant comprises a liposome.

57. A chimeric polypeptide comprising a first domain comprising a polypeptide as set forth in claim 1 and a second domain comprising a cell membrane permeant, wherein the polypeptide when administered to or expressed in a cell disrupts the G2 cell cycle arrest checkpoint.

58. The chimeric polypeptide of claim 57, wherein the polypeptide is a recombinant fusion protein.

59. An isolated or recombinant nucleic acid encoding a polypeptide as set forth in claim 1 or claim 57, wherein the polypeptide when administered to or expressed in a

60. An expression vector comprising a nucleic acid encoding a polypeptide as set forth in claim 1 or claim 57, wherein the polypeptide when administered to or expressed in a cell disrupts the G2 cell cycle arrest checkpoint.

61. A cell comprising a nucleic acid encoding a polypeptide as set forth in claim 1 or claim 57, wherein the polypeptide when administered to or expressed in a cell disrupts the G2 cell cycle arrest checkpoint.

62. The cell of claim 61, wherein the cell is a bacterial, a yeast, an insect, or a mammalian cell

63. A pharmaceutical composition comprising a

a polypeptide as set forth in claim 1 or claim 57, wherein the polypeptide when administered to or expressed in a cell disrupts the G2 cell cycle arrest checkpoint,

a nucleic acid encoding a polypeptide as set forth in claim 1 or claim 57, wherein the polypeptide when administered to or expressed in a cell disrupts the G2 cell cycle arrest checkpoint,

an expression vector comprising a nucleic acid encoding a polypeptide as set forth in claim 1 or claim 57, wherein the polypeptide when administered to or expressed in a cell disrupts the G2 cell cycle arrest checkpoint, or

a cell comprising a nucleic acid encoding a polypeptide as set forth in claim 1 or claim 57, wherein the polypeptide when administered to or expressed in a cell disrupts the G2 cell cycle arrest checkpoint; and,

a pharmaceutically acceptable excipient.

64. The pharmaceutical composition of claim 63 comprising a liposome.

65 A method for inhibiting a the activity of a Chk1 kinase or a Chk2

the activity of the Chk1 or Chk2 kinase.

66. A method for disrupting a cell G2 cell cycle arrest checkpoint comprising contacting the cell with a polypeptide as set forth in claim 1 or claim 57 or a pharmaceutical composition as set forth in claim 63, in an amount sufficient to disrupt the G2 cell cycle arrest checkpoint.

67. A method for sensitizing a cell to a DNA damaging agent comprising contacting the cell with a polypeptide as set forth in claim 1 or claim 57 or a pharmaceutical composition as set forth in claim 63, in an amount sufficient to disrupt the G2 cell cycle arrest checkpoint, thereby sensitizing the cell to the DNA damaging agent.

68. The method of claim 67, wherein the cell is a human cell.

69. The method of claim 67, wherein the cell is a cancer cell.

70. A method for selectively sensitizing a cell with an impaired G1 cell cycle arrest checkpoint to a DNA damaging agent comprising contacting the cell with a polypeptide as set forth in claim 1 or claim 57 or a pharmaceutical composition as set forth in claim 63, in an amount sufficient to disrupt the G2 cell cycle arrest checkpoint, thereby sensitizing the cell to the DNA damaging agent.

71. The method of claim 70, wherein the cell is a cancer cell.

72. A method for inducing apoptosis in a cancer cell in an individual comprising a administering a polypeptide as set forth in claim 1 or claim 57 or a pharmaceutical composition as set forth in claim 63, in an amount sufficient to disrupt the G2 cell cycle arrest checkpoint in the cancer cell, thereby sensitizing the cancer cell to a DNA damaging agent, and administering a DNA damaging agent.

73. The method of claim 72, wherein the DNA damaging agent is 5-fluorouracil (5-FU), rebeccamycin, adriamycin, bleomycin, cisplatin, hyperthermia, UV irradiation or gamma-irradiation.

74. A method for screening for compounds capable of modulating the activity of a Chk1 kinase or a Chk2 kinase comprising the following steps

(a) providing a test compound;

(b) providing a Chk1 kinase or a Chk2 kinase;

(c) providing a polypeptide as set forth in claim 1 or claim 57, wherein the polypeptide binds to the Chk1 kinase or the Chk2 kinase; and

(d) contacting the test compound with the kinase and the polypeptide and measuring the ability of the test compound to prevent binding of the polypeptide to the kinase.

75. A method for screening for compounds capable of modulating the activity of a Chk1 kinase or a Chk2 kinase comprising the following steps

(a) providing a test compound;

(b) providing a Chk1 kinase or a Chk2 kinase;

(c) providing a polypeptide as set forth in claim 1 or claim 57, wherein the polypeptide is phosphorylated by the Chk1 kinase or the Chk2 kinase; and

(d) contacting the test compound with the kinase and the polypeptide and measuring the ability of the test compound to inhibit or abrogate phosphorylation of the polypeptide by the kinase.

76. The method of claim 75 further comprising providing a full length human Cdc25C.

78. The method of claim 77, wherein the polypeptide is a peptide comprising from about amino acid residue 200 to about amino acid residue 250 of human Cdc25C.

79. The method of claim 74 or claim 75, wherein the polypeptide of step (c) further comprises glutathione-S-transferase.

80. The method of claim 74 or claim 75, wherein the polypeptide of step (c) is immobilized.

81. A method for screening for compounds capable of specifically inhibiting or abrogating the G2 cell cycle arrest checkpoint comprising the following steps

(a) providing a test compound and a polypeptide as set forth in claim 1 or claim 57;

(b) providing a G1 checkpoint impaired cell;

(c) contacting the cell of step (b) with the test compound or the polypeptide of step (a) and a DNA damaging treatment or an M phase checkpoint activator; and

(d) measuring the amount of DNA in the cells after the contacting of step (c) to determine if the test compound has inhibited or abrogated the G2 cell cycle arrest checkpoint, wherein the polypeptide of step (a) acts as a G2-checkpoint-inhibiting positive control.

82. The method of claim 81, wherein the amount of DNA is measured using propidium iodide and FACS analysis.

83. The method of claim 81, wherein the amount of DNA is measured after about 10 to about 72 hours after the contacting of step (c).

compound that has not inhibited or abrogated the arrest at the M phase checkpoint of the cell

cycle after contacting the cell with an M phase activator is a specific inhibitor of the G2 cell cycle arrest checkpoint.

85. The method of claim 84, wherein the M phase checkpoint activator is colchicine or nocodazole.

86. The method of claim 81, wherein the DNA damaging treatment is 5-fluorouracil (5-FU), rebeccamycin, adriamycin, bleomycin, cisplatin, hyperthermia, UV irradiation or gamma-irradiation.

ABSTRACT

COMPOSITIONS AND METHODS FOR INHIBITING G2 CELL CYCLE ARREST AND SENSITIZING CELLS TO DNA DAMAGING AGENTS

The invention provides compositions and methods for inhibiting Chk1 and/or Chk2 kinases. Also provided are compositions and methods for inhibiting G2 cell arrest checkpoint, particularly in mammalian, e.g., human, cells. The compositions and methods of the invention are also used to treat disorders of cell growth, such as cancer. In particular, the invention provides methods for selectively sensitizing G1 checkpoint impaired cancer cells to DNA damaging agents and treatments. Also provided are methods for screening for compounds able to interact with, e.g., inhibit, enzymes involved in the G2 cell cycle arrest checkpoint, such as Chk1 and/or Chk2/Cds1 kinase.